BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

(SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY)

EDITORIAL BOARD

Managing Editor, FREDERIK B. BANG

Associate Managing Editor, H. WILLIAM SCOTT, JR.

CHARLES R. AUSTRIAN
E. COWLES ANDRUS
KENNETH C. BLANCHARD
EDWARD M. HANRAHAN
JOHN EAGER HOWARD
ARNOLD R. RICH

VOLUME LXXXV

BALTIMORE
THE JOHNS HOPKINS PRESS
1949

Copyright, 1949
by The Johns Hopkins Press

HOSPITAL LIBRARY

VOLUME 85 NUMBER 1

BULLETIN of the JOHNS HOPKINS HOSPITAL

THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL
SUPPORTED BY THE DE LAMAR FUND OF THE JOHNS HOPKINS UNIVERSITY

July, 1949

OSLER MEMORIAL

Sir William Osler and Bacterial Endocarditis. WARFIELD T. LONGCOPE 1

The Clinical Course of Disseminated Lupus Erythematosus: An Evaluation of Osler's Contributions. PHILIP A. TUMULTY AND A. MCGEHEE HARVEY 47

Osler's Chronic Cyanotic Polycythemia with Splenomegaly. MAXWELL M. WINTROBE 75

A Consideration of the Banti Syndrome. PHILIP F. WAGLEY 87

PROPERTY OF THE DEPARTMENT OF PEDIATRICS & COMMUNICABLE DISEASES UNIVERSITY HOSPITALS ANN ARBOR, MICHIGAN

PUBLISHED MONTHLY

THE JOHNS HOPKINS PRESS, Baltimore-18, Maryland

Made in United States of America

COPYRIGHT, 1949, BY THE JOHNS HOPKINS PRESS

BULLETIN
OF
THE JOHNS HOPKINS HOSPITAL

MANAGING EDITOR, E. COWLES ANDRUS

ASSOCIATE MANAGING EDITOR, FREDERIK B. BANG

EDITORIAL BOARD

Charles R. Austrian — Edward M. Hanrahan
Kenneth C. Blanchard — John Eager Howard
Arnold R. Rich

All correspondence relating to the publication of papers should be addressed to The Editor, Bulletin of The Johns Hopkins Hospital, Baltimore-5, Md.

Books for review should be sent to The Editor at the above address.

Twenty-five reprints, without covers, of articles will be furnished to contributors free of cost. An order slip for additional reprints, with a table showing cost, is sent with proof.

Correspondence concerning business matters should be sent to The Johns Hopkins Press, Baltimore-18, Maryland, U. S. A.

This periodical is issued monthly. Two volumes a year are issued, each consisting of approximately 400 pages, and beginning in January and July, respectively.

Subscription price. In the United States and its possessions $6.00 per year. In Canada $6.25 per year; in foreign countries $6.50 per year. Prices for back volumes and back single numbers on application. Single numbers of the current volume, when available, $.75. Prices are net, postpaid.

New subscriptions and renewals are entered to begin with the first issue of the current volume. Should any issue of the current volume be out of print at the time the subscription order is received, the pro rata value of such numbers will be credited to the next volume, and the renewal invoice therefore adjusted accordingly.

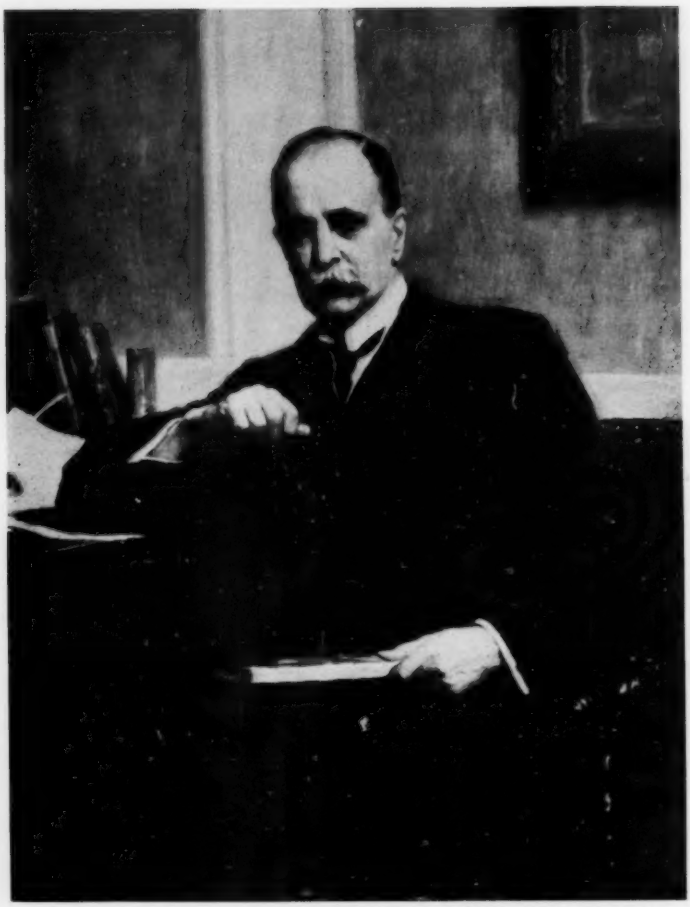
Subscriptions should be renewed promptly. To avoid a break in your series, subscriptions should be renewed promptly. The publisher cannot guarantee to supply back issues on belated renewals.

Subscriptions, new or renewal, may be sent to the Publishers or ordered through your agent.

Subscriptions in the British Empire except Canada may be sent to: Baillière, Tindall & Cox, 8 Henrietta St., Covent Garden, London, W.C. 2.

THE JOHNS HOPKINS PRESS
BALTIMORE-18, MARYLAND, U. S. A.

Entered as second-class matter at the Baltimore, Md., Post Office. Acceptance for mailing at special rate of postage provided for in Section 1103, act of October 3, 1917. Authorized on July 3, 1918.



From portrait by Seymour Thomas

Sir William Osler

July 12, 1849–December 29, 1919

Hospital Lib.
Dept.
Dr. Carl V. Weller

On several occasions, some of which are mentioned herein, Dr. Osler counseled his students and his readers to review and to weigh periodically the accumulated knowledge of disease, to find the way of future advances. One hundred years after his birth, this issue of the Bulletin of the Johns Hopkins Hospital, in the founding of which he took a special interest, contains summaries of the progress and the present status of four diseases to which Dr. Osler made particular and important contributions.

THE EDITORS

INFECTIOUS (SO-CALLED ULCERATIVE) ENDOCARDITIS.

By WILLIAM OSLER, M. D., M. R. C. P., Lond.,

PROFESSOR OF THE INSTITUTES OF MEDICINE, McGILL UNIVERSITY; PHYSICIAN AND PATHOLOGIST TO THE GENERAL HOSPITAL, MONTREAL.

UNDER the terms *diphtheritic*, *ulcerative*, *malignant*, *septic*, or *infectious* endocarditis, *arterial pyæmia*, *mycosis endocardii*, physicians now recognize one of the most formidable of cardiac affections, characterized by a peculiar morbid process on the valves, blood contaminations, constitutional symptoms of the typhoid or pyæmic types, and usually associated with multiple emboli.

It is only within the past few years that the subject has received due attention in the text-books; indeed, in some it is barely touched upon, and even in recent manuals on heart disease the account is not very satisfactory.

From the number of reported cases in French and German journals, and from the interest which the disease has excited in these countries, we might suppose it to be more common there than in England or America. A considerable number of reports, however, occur in the "Transactions of the Pathological Society of London" and in the British journals. In the leading American periodicals there are very few references, but cases have

Arch. of Medicine, *5*, 44, 1881

SIR WILLIAM OSLER AND BACTERIAL ENDOCARDITIS

WARFIELD T. LONGCOPE

It was in 1875 that Dr. Drake retired from the Professorship of "The Institutes of Medicine" at McGill University. Osler had hoped to obtain the position of demonstrator in this department, but he was now given the position of lecturer, though he was only 25 years of age, and at the completion of the semester was appointed Professor of "The Institutes of Medicine" to succeed Dr. Drake. He was thus made responsible for the rather dreary task of lecturing on Physiology and Histology.

At this time, however, there was an epidemic of small pox in Montreal and Osler spent much time in the wards of the small pox hospital. His interest in pathology led to his appointment the following year, in 1876, to the status of Pathologist to Montreal General Hospital, and two years later at the age of 28 to the important post of Physician to the Montreal General Hospital. As pathologist, during this period, he made many brief reports including those on Aneurysm, endocarditis and diseases of the heart. It was, therefore, early in his career that his intense and life-long interest arose in these subjects.

It was not until 1881, however, that his first contributions to the problem of infectious endocarditis appeared, one in the Archives of Medicine, and a second in the Transactions of the International Medical Congress in London.

In order to trace the observations that culminated eventually in the recognition of a particular form of endocarditis which is now usually designated as Subacute Bacterial Endocarditis, it is necessary to quote "in extenso" from one after another of his articles. In doing so it will be desirable to call attention to the particular observations that bear upon the development of a knowledge of this disease. It must be remembered that when these early articles appeared, bacteriology was in its infancy and Koch's discoveries, with his monumental work on the tubercle bacillus, had not been published.

Abstracts from Osler's paper on infectious endocarditis follow:

INFECTIOUS (SO-CALLED ULCERATIVE) ENDOCARDITIS. (1)

By William Osler, M.D., M.R.C.P., Lond.

Professor of the Institutes of Medicine, McGill University; Physician and Pathologist to the General Hospital, Montreal

(Arch. Med. 1881; *5*: 44)

"Under the terms *diphtheritic*, *ulcerative*, *malignant*, *septic*, or *infectious* endocarditis, *arterial pyaemia*, *mycosis endocardii*, physicians now recognize one of the most formidable of cardiac affections, characterized by a peculiar morbid process on the valves, blood contaminations, constitutional symptoms of the typhoid or pyaemic types, and usually associated with multiple emboli.

It is only within the past few years that the subject has received due attention in the text-books; indeed, in some it is barely touched upon, and even in recent manuals on heart disease the account is not very satisfactory.

From the number of reported cases in French and German journals, and from the interest which the disease has excited in these countries, we might suppose it to be more common there than in England or America. A considerable number of reports, however, occur in the "Transactions of the Pathological Society of London" and in the British journals. In the leading American periodicals there are very few references, but cases have been reported by Ellis,* Lomax,† Pepper,‡ Keating,§ and Peabody.¶

With regard to the nomenclature, I think the terms *infectious* and *septic*, as given by Jaccoud,‖ better than the others. Against the name *ulcerative* is the fact that there may be no actual ulceration on the valves, and there may be, on the other hand, endocardial losses of substance without the special constitutional disturbances by which the disease is characterized. The term *diphtheritic* is good, in so far as it expresses a resemblance in the histological features of the valvular disease to that of true diphtheritic exudation, but this is scarcely sufficient ground for its use; and it is, in a way, misleading, indicating a relation between diphtheria and the disease, which is not known to exist. The name *mycosis endocardii* certainly expresses a striking feature of the local process, but with our present imperfect knowledge of the relation of the micrococci colonies to the disease, such a designation is, to say the least, premature. On the other hand, the term *infectious* presupposes no special view as to the nature of the local process, and at the same time indicates, as Jaccoud says, a constant and exclusive character of the disease.

---

* *Boston Med. and Surg. Journal*, Nov. 15, 1877.

† *Philadelphia Medical and Surgical Reporter*, 1874.

‡ *American Journal of Medical Sciences*, 1871.

§ "Transactions of the College of Physicians of Philadelphia," 1879.

¶ *New York Med. Record*, 1880.

‖ Pathologie Interne, tome i, and Nouveau Dictionnaire, tome iii.

It would appear that, clinically, three classes of cases are included in the disease known as ulcerative endocarditis, and I think it important that a distinction should be made between them. We have:

1. Those cases in which the disease appears without any obvious cause, either spontaneously or in connection with rheumatism or some other affection. The term *infectious* might be applied to this class. It is the *arterial pyaemia* of Wilks, the primary ulcerative endocarditis of some authors.

2. Those in which the endocardial disease is secondary to some inflammatory focus—acute necrosis, puerperal endometritis, etc. To these the term *septic* might be applied.

3. In certain cases of chronic valvular disease an acute endocardial process may be engrafted (recurrent endocarditis), presenting anatomical features similar to the infectious form, but not characterized by the same clinical picture, the patients dying with the symptoms of chronic heart disease.

The following paper embodies my experience of this disease. The chief points to which I wish to call attention, and which are illustrated by the cases, are:

1. That the majority of cases of infectious endocarditis occur independently of rheumatism.

2. To the frequency with which infectious endocarditis is associated with pneumonia.

3. The production of acute multiple aneurisms of the aorta in the disease.

4. To certain histological features in the endocardial vegetations, and particularly to a remarkable fungoid growth met with in one of the cases."

After the introduction there follow histories and autopsy notes on seven cases of "Infectious Endocarditis." Cases 1, 2, 3, 4 and 6 are clearly instances of pneumonia complicated by an acute and rapidly fatal endocarditis.

The fifth case is also considered to be one of pneumonia, but the autopsy disclosed certain interesting features. The vegetations involved, not only the aortic valves but the wall of the left ventricle below them. In addition to this the note is made that the aortic valves were bicuspid. Though Osler interpreted the pulmonary lesions as those of a resolving pneumonia, the general clinical and pathological picture with the plaque of vegetations plastered upon the wall of the ventricle below the aortic valves, as well as the multiple aneurysms of the ascending aorta which contained vegetations, are all suggestive of an extensive subacute bacterial endocarditis. There might be some question, from the description given of the aortic valves whether this condition was of congenital origin, but the observation is noteworthy in view of the prominence given many years later to the occurrence

of bacterial endocarditis upon bicuspid aortic valves. For these reasons two paragraphs from the discussion of this case are quoted.

"The presence of multiple aneurisms of the aorta in Case 5 is deserving of comment, as I have not been able to find any similar observation in the literature of either ulcerative endocarditis or of aneurism.

The man had evidently been the subject of that peculiar congenital malformation of the aortic semilunar valves which results in the fusion of two segments. In this condition they are very liable to be the seat of a sclerotic endocarditis which terminates in incompetency; and I have met with two other cases in which the united curtains, when in this state, were the seat of extensive ulcerative endocarditis.* The cardiac affection was evidently of old standing, and in February, 1879, a year and four months before his death, hypertrophy, a double murmur and a thrill were noted."

Case 7 might well be considered as a possible instance of subacute or chronic bacterial endocarditis and is therefore quoted below in full.

"CASE 7.—*Sclerotic endocarditis of aortic valves, with incompetency; recent vegetations (ulcerative endocarditis).*

Annie M. L., aged 40, admitted Nov. 23d under Dr. Ross.

No history of acute rheumatism. For five or six years has suffered with shortness of breath on exertion. For the past year health has been failing, and she has had a troublesome cough. For three months has been confined to bed; dropsy has gradually come on, and for three weeks past spitting of blood. Her condition on admission was that of a patient in the advanced stage of obstructive heart disease, —great dropsy of legs, right hydrothorax, dyspnoea, lividity, cough, and bloody expectoration. A double aortic murmur was determined. She only lived for a little over two days after entering the hospital. The temperature was normal.

At autopsy *heart* was large, chambers full of dark clots. Mitral valves healthy. Left ventricle dilated and hypertropied. The aortic orifice was blocked with vegetations, and when slit open the valves were found much diseased; all the curtains were thickened, curled at the edges and foreshortened. On the ventricular faces were large grayish-yellow vegetations, closely adherent, but friable and roughened on the surface. In one mass the deposition of salts of lime had taken place on the outer part. Large patches of apoplexy in the *lungs*. No infarcts in *spleen* or *kidneys*, which were large and indurated.

This is an illustration of the third class, and perhaps such instances furnish the large proportion of the cases which go under the heading of ulcerative endocarditis."

The remainder of this article is devoted to a detailed description of the gross and microscopic appearance of the vegetations, together with

* *Virchow's Archiv.* lxii, 1875.

a brief discussion as to the significance of the "micrococcus balls" which he sees and pictures in what appear to us today to be quite crude drawings. They are described as follows:

"In the larger outgrowths the chief mass is composed of a nucleated fibrillar tissue, while in the superficial parts there are fibrinous lamination and numerous micrococci colonies. Capillary blood-vessels penetrate the deeper parts of the large masses, and along many there is a deposition of brown-red pigment. In some sections large micrococcus balls were met with 4 or 5 mm. from the surface.

The most remarkable structures in this specimen are the rounded bodies represented in Figs. 1 to 6, and which have been spoken of above as micrococcus balls. They vary very greatly in size; the majority of those in the specimen from which Fig. 1 was taken measured from 0.15 to 0.375 mm. Many are not more than .0075 mm., while at Fig. 6 one is shown which measured .1500 by .1125 mm. In places they occur in hundreds, closely set together, and often very small, as at Fig. 4. The outlines are sharply defined, but it is not certain whether they possess a definite membranous investment. They contain minute refractile granular spherules, which behave with reagents like micrococci. In some of the larger balls, as shown in Fig. 6, secondary ones can be seen.

I am not prepared at present to discuss the nature and affinities of these structures, but hope to do so on another occasion, when I shall enter more fully into the histology of the primary and secondary lesions of this disease."

He then proceeds to discuss the etiology of "Infectious Endocarditis" and points out first, the fact that primary infectious endocarditis in the majority of cases does not occur in connection with acute rheumatism, as was almost universally stated to be the case; secondly, the frequency with which this disease occurs with pneumonia; and thirdly, a point of clinical interest, namely, the occurrence of meningitis in three of his seven cases which he has analyzed.

The paper concludes with an account of the contemporary view as to the importance of micrococci as exciting agents together with his own opinion of their significance. In relation to our present knowledge of the subject it is interesting to quote the final paragraphs in full.

"With regard to the intimate pathology of this disease, it is assumed by most recent writers to be a mycosis, i.e., to be dependent upon the growth and propagation of lowly fungi on the valves with a consequent blood contamination. Certainly the minute bodies found in the endocardial vegetations correspond in their chemical and microscopical relations to micrococci. They are motionless, highly refractile spherules, less than a micro-millimetre in diameter, arranged in groups or colonies without any perceptible stroma. Acids, alkalies, ether and chloroform

have no effect upon them. These characters are supposed to afford satisfactory means for distinguishing them from granular detritus of an albuminous or fatty nature. Most writers have accepted the view that these bodies are fungoid in nature. Heller,* however, criticizes strongly the prevailing conceptions with regard to micrococci, and thinks that there are scarcely any micro-chemical agents or physical signs by which they can be distinguished from fatty detritus. He recommends soaking the tissue in 10 per-cent potash solution and then in iodine solution, 1 in 10 of spirit, which tints monads yellowish-brown, but is inert on fat granules. Sections of the vegetations in these cases, treated in this way, show the colonies stained of a brownish-yellow color.

Apart from any micro-chemical tests there are peculiarities about these masses which we do not see in any form of fatty degeneration, as the uniformity in size of the granules and their collection into large groups.

The question of the relation of the micrococci to the disease presents many difficulties, and we are probably not yet in a position to give a final answer to the problem. Klebs, and most German writers on the subject, give an unhesitating assent to the parasitic theory and suppose the micrococci to gain access either through the gastro-intestinal or respiratory systems, and they believe them to constitute the actual *materies morbi*. According to Koster† and Klebs‡ not only are these fungi present in the so-called ulcerative form, but they also exist in, and cause the development of, the ordinary warty or bead-like vegetations so frequently met with in the valves. Within the past few months I have examined four specimens of this variety of endocardial vegetation, and have been able to determine in each instance the presence of micrococci, not, it is true, in the same luxuriance, or arranged in definite colonies, but still sufficiently distinctive. In one case of mitral stenosis a fresh vegetation, when teased, showed many closely-packed spherules, some of which were, as Klebs has remarked with reference to the micrococci in this variety, larger than those met with in the ulcerative form. I was greatly struck with the resemblance which certain of these bodies, in this instance, bore to the individual elements of Schultze's granule-masses—those peculiar granular clumps common in blood of some animals and of impoverished persons. These structures are usually regarded as the *debris* of colorless blood corpuscles, but I have shown§ that they are aggregations of discoid bodies, probably living organisms of the nature of which we are still ignorant. They do not exist in the form of masses in the blood, but as isolated particles which might readily become adherent to the fresh endocardial outgrowths. I merely mention this as a point worthy of future investigation.

It matters little how the micrococci get to the valves, whether by embolism of the small vessels, as Koster supposes, or by deposition on the surface, as Klebs thinks; the question is: Are they responsible by their growth for the peculiar course

* *Virchow's Archiv.* lxii, 1875.

† *Virchow's Archiv.*, Bd. lxxii.

‡ *Archiv für Exper. Pathol. u. Pharmacol.*, Bd., ix.

§ Proceedings of the Royal Society, 1873.

and malignancy of cases of infectious endocarditis, primary or secondary? The facts of their occurrence in the verrucose form, which may not be accompanied by any symptoms, and of their abundance in the recurrent endocarditis, which attacks old sclerotic valves, are, I think, opposed to this view, for if they act as a septic poison in the one case, why should they not do so in the other? The micrococci do not appear to infest the blood in any numbers, so that they must be supposed to distil some subtle poison, "such soon-speeding gear as will disperse itself through all the veins" and profoundly disturb nutrition. The occurrence, however, of fatal septic cases, closely allied to, or identical with those in which a bacteric endocarditis is found, but in which no micrococci can be detected, either in the local process or in the blood, teaches us that the same poison may exist without the intervention of bacteria, the presence of which in any case may be only a partial phenomenon in a general infective process."

The second paper published in 1881 appears to be a condensed version of the large article which has just been reviewed, and it is only desirable to quote a few paragraphs. The first outlines the scope of the communication.

The second paragraph seems to forecast a group of cases, namely (3); the nature of which becomes clearer as Osler's studies proceed.

ON SOME POINTS IN THE ETIOLOGY AND PATHOLOGY OF ULCERATIVE ENDOCARDITIS. (2)

DR. WILLIAM OSLER, MONTREAL

(Trans. Internat. Med. Cong., London, 1881; *1:* pp. 341–346)

"Ulcerative, infectious, or diphtheritic endocarditis is an affection of unusual interest to the profession, both on account of the serious nature of the malady which it excites and of the illustration which it offers of many points in the pathology of infective processes.

Ulceration, loss of substance, on the endocardium occurs under a variety of conditions. Clinically we should, I think, recognise three classes of cases. *First*, those in which the disease appears without any obvious cause, either spontaneously or in connection with rheumatism or some other affection, as pneumonia, chorea, &c. These cases present a remarkable set of symptoms, very variable in character, but of which two chief types have been recognised—the typhoid and the pyaemic. This is the preliminary form of some writers. *Second*, those cases which arise during the existence of some local inflammatory process, as puerperal endometritis, acute necrosis of bone, &c., and in which the endocarditis is usually regarded as part of a pyaemic state and secondary to the local disease. And, *third*, the cases of ulcerative affection engrafted upon valves the subject of chronic sclerotic changes. In this latter variety no special symptoms necessarily accompany the process; the patients are usually in the last stage of chronic valvular disease.

I propose to consider briefly in the following paper some of the conditions under which the disease arises, some points in the morbid anatomy, and, lastly, make a ew remarks on the supposed relation of micrococci to the disease."

During the next few years, according to Cushing (3), Osler was working on the subject of endocarditis, collecting cases, doing autopsies, and gathering a large amount of material together. In 1883 he was made fellow of the Royal College of Physicians, and after a summer in Europe in 1884, he accepted an offer from the University of Pennsylvania to become Professor of Clinical Medicine, a post made vacant by the promotion of Dr. William Pepper to the senior Professorship of Medicine.

He was invited, about this time, to give the Gulstonian Lectures before the Royal College of Physicians, and he chose as his subject "Malignant Endocarditis." These three lectures delivered on Feb. 26th, March 3rd, and March 5th, 1885, have survived since their publication as a classical description of the disease.

The first lecture opened with a short general account of the knowledge of this condition as it then existed, and a statement that these lectures were based upon a review of over 200 cases that he had collected from the literature, supported by his own observations upon a large series of cases that he had studied in the wards of the Montreal General Hospital or at autopsy. The introduction to these lectures was as follows:

THE GULSTONIAN LECTURES,

ON

MALIGNANT ENDOCARDITIS. (4)

Delivered at the Royal College of Physicians of London, March, 1885

By William Osler, M.D.

Professor of Clinical Medicine at the University of Pennsylvania, Philadelphia

(*British Med. J.* 1885; *1:* 467; 522; 577)

LECTURE I

"Mr. President and Gentlemen,—It is of use, from time to time, to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigations

in the future. With your permission, sir, I propose to do this in the case of that most interesting disease generally known as ulcerative endocarditis, a disease the phenomena of which were first clearly explained by the late Dr. Kirkes, from whose investigations in 1851–52 we date our accurate knowledge of the affection. Some of those who listen to me today can doubtless recall, and recall with pleasure, the Gulstonian Lectures of 1851, in which Dr. Ormerod dealt so fully and so ably with valvular affections of the heart; but a reference to them will show how much the past twenty-five years have done to widen our view of cardiac disease, more particularly in regard to the effects of emboli, and the association of valvular inflammation with grave constituional disorder, and the probable connection of the disease with the presence of micro-organisms. By the labours of Drs. Ogle, Wilks, Simpson, Moxon, Bristowe, and others in this country, of Charcot, Vulpian, and Lancereaux in France, and of Virchow and a host of observers in Germany, a large amount of material has been accumulated; and we may assume that the etiological, clinical, and anatomical characters of the disease have been fairly well ascertained, and that we have got about as far towards a full knowledge of the affection as the ordinary means at our disposal will permit. The inquiry now enters upon another stage, and it remains for experimental investigation to determine, if possible, the relation of the endocarditis to those diseases with which it is most frequently associated. This being the case, the present time has seemed to me a favourable opportunity to summarize our knowledge to date; and, for this purpose, I have reviewed the records of over two hundred cases, which, from the description of the symptoms and lesions, were evidently of the type of malignant endocarditis; and these, with the considerable experience I have had at the General Hospital at Montreal, may perhaps enable me to give a somewhat more comprehensive account, in some respects, than has yet been attempted."

He then points out the difficulties of classification and nomenclature and finally defines the types of malignant endocarditis as follows:

"Malignant endocarditis occurs under the following conditions: 1, as a primary disease of the lining membrane of the heart or its valves, either attacking persons in previous good health, or more often attacking the debilitated and dissipated, or those with old valve-lesions; 2, as a secondary affection in connection with many diseases, particularly rheumatic fever, penumonia, scarlet fever, diphtheria, ague, etc.; 3, as an associated condition in septic processes, traumatic or puerperal. We shall discuss first the anatomical characters, then the clinical features, and lastly the etiological and pathological relations."

He then goes on to describe the gross pathological and histological characteristics of the lesion.

The following paragraph concerning the relationship of micrococci to these lesions is, today, of some interest for he states

"The micrococci are constant elements in the vegetations. All granules of an uniform size met with in the sections are not micro-organisms, nor, indeed, are all which stain by some methods recommended for the detection of these bodies. By far the most satisfactory method is that of Gramm (*Fortschritte der Medicin*, Band i, Berlin), in which the section, after staining in gentian-violet, is transferred for a few minutes to a dilute solution of iodine and iodide of potassium, and then to the alcohol, when it is found that the colour has been extracted from all tissue-elements and nuclei, leaving only the micro-organisms stained. They vary a good deal in number and arrangement, and may be scattered singly in the granular substance or arranged in groups. They are usually very numerous at the deeper part of the vegetations, just where the structureless material joins the granulation-tissue, and they may penetrate deeply into the substance of the valve. Sometimes the smaller vegetations seem made up exclusively of them. Several of my specimens appear to confirm the view of Klebs (*Archiv für Experiment. Pathologie*, Band vi), that the micrococci lodge first on the endocardium, and penetrate into the substance, often as distinct columns. In their immediate vicinity, there is a zone of necrosis, and beyond this an accumulation of leucocytes and signs of reactive inflammation. The micro-organisms found in connection with the malignanat endocarditis are not all of the same kind. Klebs distinguishes two forms, one met with in septic, and the other in rheumatic, cases. In some instances, the micrococci are all arranged in zoogloea-like masses; in others, particularly the septic cases, they are in chaplets. Some present distinct capsules. Small elongated bacilli have also been found; I have seen them in one instance, short stout rods, often joined in pairs."

The frequency with which he found the different valves of the heart affected is of interest and the fact that the endocardium of the ventricles was involved in 33 cases is noteworthy since this finding is so reminiscent of subacute bacterial endocarditis.

"The following figures give an approximate estimate of frequency with which different parts of the heart are affected. The aortic and mitral valves were affected together in 41 cases, the aortic valves alone in 53, the mitral alone in 77, the tricuspid in 19, the pulmonary valves in 15, and the heart-wall in 33. The right heart is rarely affected alone; this occurred in only 9 instances, in 5 of which the tricuspid, and in 4 the pulmonary, valves were involved. The valves are most often attacked along the lines of closure, as in the simple endocarditis; the auricular faces of the mitral flaps and the ventricular surfaces of the aortic cusps suffering most severely. Mural endocarditis is most often seen at the upper part of the septum of the left ventricle, just below the aortic ring, in which situation some of the most extensive and deep cardiac ulcers occur, leading to perforation of the septum. Next in order is the endocardium of the left auricle on the postero-external wall, as noted by Lepine (*Bull. de la Soc. de Biologie*, 1869)."

Of some significance, also, is the paragraph dealing with the relative

frequency with which the acute process is engrafted on valves that are chronically diseased.

"It was Sir James Paget (*Medico-Chirurgical Transactions*, vol. xxvii), I think, who first referred to the frequency with which sclerotic and malformed valves are attacked by acute disease. Chronic valvulitis is met with in a large number of cases of malignant endocarditis. The records which I have examined give only a percentage of about twenty-five; but the condition of the valves, except as regards ulceration, was often omitted, and thus represents a very much smaller percentage than actually occurs. In more than three-fourths of the Montreal cases, sclerotic changes were present; and Dr. Goodhart found (Pathological Society's *Transactions*, vol. xxxiii), in a series of sixty-nine cases, that sixty-one presented old thickening of the valves. In very many of the cases, the condition of fusion of two of the aortic cusps was present. This abnormality is almost invariably accompanied by sclerotic changes, and to the existence of these is probably due the frequency with which they are attacked by ulceration. In seventeen instances of fusion of two of the aortic cusps of which I have notes, there were ulcerative changes in eight, in two or three of an atheromatous nature."

Later he pays particular attention to the embollic phenomena that often accompany the disease, and refers specifically to the frequency of hemorrhages in the skin.

". . . In the group of primary cases, the lesions are entirely those of endocarditis, local and general. In the second place, there are the extensive pathological changes due to embolism; and these constitute interesting features in the disease, and may produce a very great variety of lesions in every portion of the body. I do not propose to deal very fully with these, but to call attention only to some special points. The cases may be divided into those without any embolic processes, cases in which the infarcts are simple, not suppurative, those in which there are innumerable suppurative infarcts and cases in which some of the infarcts are simple and some suppurative. It is remarkable how variable these embolic features are. They may be entirely absent in well marked malignant cases. They are not necessarily associated with suppuration; indeed, in a very considerable number of cases, they present the characters of ordinary hemorrhagic infarcts, but in the traumatic and puerperal cases the infarcts are invariably septic. They may be few in number, only one or two perhaps in the spleen or kidney, or they may be in thousands throughout the various organs of the body. When suppurative, micrococci, in my experience, are always present; but the micrococci may exist in the vessels without inducing this change. In severe forms of the disease, haemorrhages are very frequent upon the skin, and on the serous and mucous surfaces. The cutaneous ones will be referred to again in connection with the symptomatology. They appear, in many instances, to be due to the effect of the poison, just as in other

infectious diseases; in others, they are undoubtedly embolic, and a minute necrotic or suppurative centre can sometimes be seen. . ."

The first lecture ends with a rather detailed description of the pathological appearance of these complications as well as others of a different nature such as meningitis.

The second lecture, devoted to a description of the clinical features of the disease, opens with an introductory statement

THE GULSTONIAN LECTURES,

ON

MALIGNANT ENDOCARDITIS

Delivered at the Royal College of Physicians of London, March, 1885

By William Osler, M.D.

Professor of Clinical Medicine at the University of Pennsylvania, Philadelphia

LECTURE II

"*Symptoms.*—In considering the symptoms of endocarditis, it is important to bear in mind the manifold conditions under which the disease may develop. A limited number of cases may be grouped together as forming a primary substantive disease; but in the great majority the affection is either an associated pathological state, or is of the nature of a secondary malady arising in the course of some other disease. . . ."

This is followed by a discussion of the modes of onset in which again the embolic complications are stressed, and both retinal hemorrhages and hematuria are referred to. Attention is also directed to the ague types of fever, which, in later communications, plays an important role.

"The different modes of onset, and the extraordinary diversity of symptoms which may arise, render it very difficult to present a satisfactory clinical picture. The general symptoms are those of a febrile affection of variable intensity, which may be ushered in, like any acute fever, with rigors, pain in the back, vomiting, headache, etc. Arising in the course of some other disease, there may be simply an intensification of the fever, or a change in its features. The pyrexia is constant, but variable in type and intensity, and more likely than any other symptom to lead to misinterpretation. Prostration of strength, delirium, sweating, and other signs of severe constitutional disturbance, are usually present.

Cardiac symptoms may be marked from the outset; pain, palpitation, sense of distress, and murmur; in many instances, there has been old valvular disease, but

in a considerable number of cases the heart-symptoms remain in the background, hidden by the general condition, and giving no indication; or they may be so slight, that they are not even detected on special examination.

The embolic processes give a special prominence to local symptoms, which may divert attention from the general malady. Thus delirium, coma, or paralysis may arise from implication of the brain or its membranes; pain in the side and local peritonitis from involvement of the spleen; bloody urine and pain in the back from affection of the kidney; loss of vision from retinal hemorrhages; and suppuration in various organs, or gangrene, from the distribution of emboli.

So diverse are the features of malignant endocarditis, that a consideration of the symptoms is greatly facilitated by arranging the cases in groups, according as they display special characters. Dr. Kirkes, in 1852, called the attention of the profession to the occurrence of a typhoid-like condition in acute endocarditis, and he subsequently pointed out the fact that inflammation of the valves might lead to pyaemia. The investigations of Charcot and Vulpian (*Gazette Médicale de Paris*, 1862), of Virchow (*Gesammelte Abhandlungen*), of Jaccoud (*Nouveau Dictionnaire de Médicine*, etc., art. Endocarditis), and others, gradually led to the recognition of these two great types of the disease. Of late, still further separation has been made of the cases with features closely resembling ague or intermittent, and also of cases in which the cardiac symptoms are most prominent; and I shall call attention to certain cases in which the symptoms are those of an acute affection of the cerebro-spinal system. . . ."

A little later in the lecture considerable space is devoted to an account of this ague type of the disease which Osler notes may be prolonged for several months.

"But by far the most remarkable cases of the pyaemic group are those which present a marked intermittent type of pyrexia, simulating a quotidian or tertian ague. They may occur without any signs or indications of heart-disease, or the symptoms may develop in individuals the subjects of chronic valvulitis. The cases are not nearly so frequent as those of the typhoid type; but they have been specially studied by Drs. Wilks, Bristowe, and Coupland in this country, Lanceraeux in France, Leyden and others in Germany. The paroxysms may have the absolutely typical features of intermittent; the chills, hot stage, and sweating succeeding each other with regularity; and in the intervals there may be an entire absence of the fever. The quotidian type is the most common; the tertian has occasionally been described; and in rare instances two paroxysms have recurred within the twenty-four hours. The cases may be much prolonged, even for three or four months. One of the first references I find to cases of this kind is in a footnote to one of Dr. Ormerod's Gulstonian Lectures (*Medical Gazette*, 1851), in which a case of Dr. Bond of Cambridge is narrated—an instance of chronic valvular disease, with intermittent fever and diarrhoea, two paroxysms occurring in the day. The case lasted four months. In a remarkable case (Dr. Ray) described by Dr.

Wilks (BRITISH MEDICAL JOURNAL, 1868), during a six or seven weeks' illness, rigors recurred with such regularity that a tertian ague was suspected for a time, although the patient was known to be the subject of heart-disease. In some instances, the existence of ague previously has rendered the condition much more puzzling. In several of Lancereaux' cases (*Gazette de Médicine*, 1862; *Archives Générales*, 1873), the patients had had intermittent fever a short time before; so also with one of Leyden's cases (*Zeitschrift für Klin. Med.*, Bd. iv, Berlin). But the most extraordinary case of the kind is recorded by Dr. Bristowe (*British Medical Journal*, 1881). A patient had ague in October, chills once or twice a day; she was ill for six weeks; and, after an interval of two or three weeks, they recurred in the second week of December, and continued until December 23rd. She was well for a few days, and then the attacks recurred after sleeping in a cold bed, and persisted until her admission to hospital on February 12th. For the four weeks previous to entrance, the attacks came every twelve hours regularly. A murmur was noticed; but the history of ague was so clear, and the attacks so characteristic, that a suspicion of malignant endocarditis was at first not entertained. It was only after the failure of quinine and a variation in the character of the paroxysms, that a diagnosis was reached. In Dr. Coupland's cases (*Med. Times and Gazette*, 1822, vol. i), the intermittent pyrexia was also well marked. In none of our Montreal cases was the aguish type very pronounced, though in one or two cases there were regularly recurring paroxysms of chills, fever, and sweating; but the conditions under which the attacks developed rendered the clinical features more like ordinary pyaemia. The majority of these cases appear to arise independently of other affections, and occur among what I have referred to as the primary class of cases; though, as already mentioned, some develop in chronic valvular disease, and others appear associated in some way with ague."

The following cases illustrate the chief features of this form.

"Ann O., aged 46, large well nourished woman, was admitted under Dr. Wilkins, June 5th, 1881. She had been a healthy woman. Dr. Blackader saw here on the 2nd, when she complained of severe pains in the back, loins, and hips, which were relieved by poultices. Pulse rapid, tongue furred, no diarrhoea. She was supposed to be suffering from typhoid fever. No reliable history, family or personal, could be obtained, but she had been out of sorts for four or five days previous to the onset of the attack. On admission, temperature 104°; pulse 110; respiration 32; no eruption; lungs normal; no heart-murmur; no albumen in urine. On the 6th, she passed a restless night. Temperature, 104°; pulse 120, dicrotic; abdomen distended; two stools. She passed 18 ozs. of urine, slightly bloody, which might have been from the menses, which began to-day. On 7th, morning-temperature 103.2°; pulse weak, 120; respiration 54, shallow; loud sonorous *râles* over chest; bowels and bladder emptied involuntarily; stools frequent, high coloured; patient could not be roused. The legs and general surface seemed tender, which caused her to cry out when moved. Urine drawn off by catheter contained much blood,

50 per cent. by volume of albumen, and many granular casts. Pupils unequal; head drawn to the right. Some rigidity of muscles of arms, most marked on the left; increasing coma, and death at 3.30 P.M. of the 7th, the sixth day of her serious illness. At necropsy, no hypertrophy of heart; mitral valves a trifle thick, with small superficial losses of substance on both curtains. Aortic valves normal; infarcts in spleen. Numerous small haemorrhagic emboli in kidneys and throughout the intestines. Six or eight suppurating infarcts in brain, chiefly near longitudinal fissure and on median surfaces. The case is a good example of the primary malignant endocarditis occurring in a healthy individual, and running a rapid course, with symptoms of typhoid character. The diarrhoea was not profuse, though the intestinal lesions were well marked."

There then follow descriptions of acute cases occurring during the course of pneumonia or in pyaemia, but in the next group termed "Cardiac Group" Osler refers to cases that remind one very forcibly of instances of subacute or even chronic bacterial endocarditis.

"*Cardiac Group.*—Under this heading may be arranged, as suggested by Dr. Bramwell (*Diseases of the Heart*), those cases in which patients, the subjects of chronic valve-disease, are attacked with febrile symptoms and evidences of a recent endocarditis engrafted upon the old process. I have already remarked on the great frequency with which ulcerative changes are found in connection with sclerotic endocarditis. Many of such cases present features of the pyaemic, typhoid, or cerebral types, and may be of the most acute character; but, in others, the process appears much less intense, and the cause more chronic. In a considerable series of cases, the history is somewhat as follows. The patient has, perhaps, aortic valve-disease, and is under treatment for failing compensation, when he begins to have slight irregular fever, an evening exacerbation of two or three degrees, some increase in cardiac pain, and a sense of restlessness and distress. Embolic phenomena may develop; a sudden hemiplegia; pain in the region of the spleen, and signs of enlargement of the organ; or there is pain in the back, with bloody urine. In other instances, peripheral embolism may take place, with gangrene of the foot or hand. There may be hebetude or a low delirium. Instances such as these are extremely common; and while, in some, the process may be very intense, in others the term malignant seems not at all applicable to them; still, in a large series of cases, all gradations can be seen between the most severe and the milder forms. Dr. Green (*Lancet*, 1884, vol. i) referred to a case which lasted six months, and to another in which, during eighteen months, there were attacks of irregular fever. I have known the febrile symptoms subside for weeks, to recur again with increased severity; and there are cases which render it probable that the process may subside entirely. The ulcerative destruction, in these cases, may be most extensive; and I have seen the aortic ring with scarcely a trace of valve-substance left. The process in the chronic cases is also mycotic, and it is to be

carefully distinguished from the atheromatous changes. In very many instances, there is no history of rheumatic fever or of other constitutional disorder; but the endocarditis appears to attack the sclerotic valves as a primary process, and a very considerable number of the most typical cases are of this kind. A good example was the following case, in which the disease attacked peformed and hardened valves, and the clinical symptoms were prolonged for nearly three months.

H. M., aged 38, was admitted September 8th, under Dr. Ross. He had a good family and personal history; he had always enjoyed excellent health. A month ago he had chilly feelings, fever, and sweating, with vomiting. He kept about until ten days before admission, when he took to bed, with pains at the heart, and fever. On admission, there was marked aortic incompetency; temperature 100° Fahr.; he seemed dull and heavy. On 15th, there was iliac tenderness, and some diarrhoea. For the next two weeks, he remained in same state, temperature rising at times to 103° Fahr. During the first week of October, the prostration increased, and there was slight delirium at night; temperature not higher than 102° Fahr. On the 14th, there was an eruption of petechiae. From this time, the temperature kept lower—100° to 101° Fahr.—the delirum and prostration increased, and death took placed on the 23rd. Two of the aortic cusps had fused, and there were old sclerotic changes; there were recent soft greyish vegetations; the spleen presented six or eight infarcts, one suppurative.

These are the cases of ulcerative endocarditis which present fewest difficulties in diagnosis. The existence of the chronic heart-disease excites attention; and even if compensation has previously been perfect, the ulcerative process may be the very cause of disturbing the balance and producing marked symptoms. In my experience, the existence of fever is invariable when the ulcerative processes are due to micrococci, whereas most extensive destructive changes may occur in atheromatous disease without any elevation of temperature. It may be possible that the granular detritus discharged from atheromatous foci on the valves, or on the aorta, may have irritating properties; yet, in two instances, I have met with most extensive atheromatous ulcers on valves and aorta, from which large quantities of material must have been discharged, and the patients were not febrile. Dr. Sansom (*Lancet*, 1884, vol. i), however, has referred to a case of ulcerative endocarditis in which there was no elevation of temperature throughout."

The so-called "cerebral group" which follows, is composed principally of cases running an acute course with cerebra-spinal meningitis.

In the description of the cutaneous lesions definite reference is made to "petechiae."

"The occurrence of a rash has been described by many observers and, in some instances, has led to errors of diagnosis. The most common form is the hemorrhagic, in the form of small petechiae, distributed over the trunk, particularly the abdomen, less often in the face and extremities. They may be most abundant over the whole

body, and at times are large and present small white centres. When severe nervous symptoms are also present, the resemblance of the cases to cerebro-spinal meningitis, or typhus, may be very close. In one instance, the case was thought to be haemorrhagic variola (Duget and Hayem, *Comptes rendus de la Soc. de Biologie*, 1865). An erythematous rash has also been observed.

In a case of Dr. Cayley's (*Lancet*, 1844, 1), there was a mottled red rash on the skin. Colson (*Bull. de Soc. d'Anatomie*, 1876) describes a case in which the rash was erythematous, and in spots distinctly papular. . . ."

This lecture ends with a paragraph alluding to the variable course of the disease, and again Osler makes passing reference to the cases lasting two to three months.

"The course of the disease presents many variations, well illustrated by the records I have given; very acute cases may run their course within the week, as in the patient Ann O., already referred to, while in others the duration may be even two or three months. Except in certain cases in which the patients are the subjects of chronic valvulitis, the course is rarely prolonged byond four or five weeks."

The third and last lecture starts with a paragraph emphasizing the difficulties of diagnosis.

THE GULSTONIAN LECTURES,

ON

MALIGNANT ENDOCARDITIS

Delivered at the Royal College of Physicians of London, March, 1885

By William Osler, M.D.

Professor of Clinical Medicine at the University of Pennsylvania, Philadelphia

LECTURE III

"*Diagnosis.*—Few diseases present greater difficulties in the way of diagnosis, difficulties which in many cases are practically insurmountable. It is no disparagement to the many skilled physicians who have put their cases upon record to say that, in fully one-half of them, the diagnosis was made *post mortem*. In spite, too, of able memoirs in the journals, the disease has not been much known, and it is only of late years that the text-books have contained chapters upon it. The protean character of the malady, the latency of the cardiac symptoms, and the close simulation of other disorders, combine to render the detection peculiarly difficult.

In the group of cardiac cases in which the disease attacks a patient the subject of chronic valvulitis, the matter is usually easy enough. The existence of fever of an irregular type, and the occurrence of embolism, generally suffice to make the

case clear. It must be remembered that simple warty endocarditis not unfrequently attacks sclerotic valves, and may be accompanied by slight fever. Of course, in chronic heart-disease, irregular pyrexia may arise from other causes—local suppuration, cellulitis, etc.—which must be excluded. . . ."

Among these difficulties, as Osler points out later, one relates to the resemblance that certain types of this disease bear to malaria.

"It seems strange that difficulties should arise in the diagnosis between malaria and malignant endocarditis, but the records of cases plainly show that for weeks or months a condition of intermittent pyrexia may occur, simulating every type of ague. The paroxysms in regularity, in order of sequence, and in the accompanying general conditions, may fulfil every condition of a quotidian or tertain intermittent; and the development of cardiac symptoms, with breathing of the pyrexial type, may alone determine the nature of the case."

In the long discussion devoted to the etiology of infective endocarditis, rheumatism assumes a prominent position. But it does so, not as much on account of its being an immediate cause of the acute disease, as by reason of the fact that some of the patients gave a history of having had a previous attack.

"In 127 of the cases, the endocarditis was associated with other diseases, some of the most important of which we shall now proceed to consider.

Rheumatism.—Since Bouillaud called special attention to the frequency of cardiac complications in this disease, its importance in the etiology of endocarditis has been universally recognised. And, as regards the simple form of endocarditis, the general statements are quite true, but, fortunately, the graver and fatal form is much less common, much less, I think, than is usually supposed. In 53 cases, there was a history of rheumatism, past or present. I included every case in which there had been the record of an attack, recent or remote. In only 24 did the symptoms of severe endocarditis arise during the progress of the acute or sub-acute disease. In 29 cases, there was simply a history of rheumatism, often years before, and no mention of the occurrence of joint-troubles at the time of the development of the endocarditis. Dr. Ogle called attention to the fact that ulcerative endocarditis occurred very often in persons in whom no rheumatic history could be traced. Of 21 cases which he reported, some of which were probably atheromatous, in only 3 was rheumatism mentioned. In only 3 also of the Montreal cases was there any positive history of rheumatism, either before or during the attacks. The following case, under the care of Dr. Ross, is a good example of the mode of onset. . . .

"In a larger number than in any other group, sclerotic valves were found, with the existence of which the past rheumatism could, in many instances, be connected.

A primary rheumatic endocarditis was recognised by Latham, also by Graves and Stokes, and it is quite possible that some of the cases which I have grouped as protopathic represented instances of the kind in which, if life had been prolonged, joint-troubles might have supervened."

The final paragraphs give some conception of the difficulty encountered in solving the etiology of such a complicated situation at a time when the science of bacteriology was in its infancy.

"Briefly stated, the theory of acute endocarditis which at present prevails, and the only one to which I shall refer, is, that it is in all its forms, an essentially mycotic process; the local and constitutional effects being produced by the growth on the valves, and the transference to distant parts of microbes, which vary in character with the disease in which it develops. This very attractive theory can be adjusted to meet every requirement of the case, though as yet lacking certain of those substantial data necessary for full acceptance, but which, having been furnished of late years in other diseases, we may reasonably hope will in time also be forthcoming for this. . . .

In the way of experimental investigation of the properties of the micrococci, not much has been done of a satisfactory nature. Heiberg (Virchow's *Archiv*, Band lvi) placed bits of vegetations from a puerperal case beneath the skin and in the peritoneal cavity of a rabbit without effect. Eberth (*Ibid.*, Band lvii), Birch-Hirschfeld (*Archiv der Heilkunde*, Band xvii), have produced panophthalmos in the rabbit by inoculating the cornea; and I was able to produce well marked mycotic keratitis in the same animals with fresh material from the valves of two cases. H. Young, of Manchester, inoculated rabbits with pus from an abscess in ulcerative endocarditis, and was able to detect micrococci in the blood.

No conclusive culture-experiments have yet been made. Grancher (*Journal de Médicine de Paris*, December 20th, 1884) has cultivated a microbe from the blood, taken during life with all necessary precautions, but apparently not in series, and no inoculations of animals were made. Cornil (*L'Abeille Médicale*, December 22nd, 1884) has made cultures on gelatine, but apparently no special results have been reached. . . .

. . . In the first place, we do not yet know, with sufficient accuracy, the frequency of the occurrence of microbes in simple endocarditis. Are they constantly present, or only in forms associated with special diseases? Secondly, we want full information of the various forms of micro-organisms occurring in secondary endocarditis, and of their relation to the microbes assumed to be the cause of the primary disease. And, thirdly, we are only at the threshold of inquiries relating to the culture of these organisms, to the macroscopic characters of their growth, and to the possible experimental production of endocarditis."

These lectures remain today a classical contribution to the subject of infectious endocarditis. They incorporated all the knowledge that

was then available concerning this subject, and were still further illuminated by Osler's personal observations. He correlated this information and classified it as well as it could be done at a time when bacteriology was in an embryonic state. Though, perhaps, a majority of the cases were instances of acute infectious endocarditis, several could now be interpreted, from the description which Osler gives, as examples of subacute bacterial endocarditis. The preexisting valvular lesions, the prolonged course with irregular or intermittent fever, the subjective symptoms, the petechial hemorrhages in the skin, the retinal hemorrhages, enlarged spleen, the hematuria and the presence of multiple and non-suppurative infarcts are all characteristic of this condition.

In the year following the Gulstonia Lectures Osler published an important paper which is rarely referred to. It was entitled "The Bicuspid Condition of the Aortic Valves" (5) and appeared in the first volume of the Transactions of the Association of American Physicians. He defines the condition as follows:

THE BICUSPID CONDITION OF THE AORTIC VALVES

By William Osler, M.D.,F.R.C.P., Lond.

Professor of Clinical Medicine in the University of Pennsylvania

(Trans. Assoc. Am. Physicians 1886 *i;* 185–192)

"*Definition.*—A condition of the arterial valves in which two of the cusps are more or less perfectly fused, so that the orifice is guarded by only two segments.

Frequency of the Occurrence.—It is usually referred to as a common abnormality, and Dilg[1] has tabulated 64 cases in the pulmonary, and 23 in the aortic, valves. A careful study of the anomaly has recently been made by Martinotti and Spernio,[2] and again by Martinotti,[3] who remarks that the list given by Dilg of the condition in the aortic valve might be greatly extended. In over eight hundred autopsies, I have met with it in 18 cases, 17 in the aortic valves, and in 1 case in both aortic and pulmonary valves. A detailed account of the cases is given in the appended table. In 110 cases of valvular disease of all kinds, there were 57 in which the aortic segments were affected, either alone or in conjunction with the mitral and tricuspid valves; so that this condition was present in over thirty per cent. of all the cases of aortic disease, a proportion which I am inclined to regard as exceptional."

---

[1] Virchow's Archiv, xci.

[2] Atti della R. Academia di Medecina di Torino, 1884, reprint.

[3] Gazzetta delle Cliniche, 1886, reprint.

He then goes on to say that the aortic valves in 8 of his 18 cases were the seat of an infectious endocarditis, a matter to which he had referred in an earlier paper. He now elaborates still further this statement.

"*Clinical Features.*—In two of the Cases (2 and 14) the condition was found after death and there was no evidence that the persons had suffered from cardiac symptoms. Cases 5 and 10 died suddenly, and in Case 4 death was also sudden but resulted from the ruputure of a cerebral aneurism. Excluding Case 7, a foetus, the remaining twelve cases presented the clinical features of heart disease. In eight there was ulcerative endocarditis, in Cases 7, 9, 13, and 18 of a very severe type. Cases 1, 11, 15, and 16 were examples of gradual heart failure with the usual symptoms of disturbed compensation. Thus in fifteen[1] of the cases the cause of death could be attributed directly or indirectly to the existence of this anomaly. Whether the result of foetal endocarditis or a primary failure in development, the condition thus plays an important part in the history of aortic valve disease. The special proneness of mal-formed structures to disease in well known, and the conjoint segments are rarely, in the adult, free from sclerotic changes, while in nearly half of my cases there was also ulceration. Doubtless, the strain upon the fused curtains is more severe than upon normal cusps, and though in the foetus, and even in the adult, the tissue of the valve may have the natural thinness and mobility, yet, as a rule, there are induration and thickening. I have elsewhere[2] called attention to the frequency with which ulcerative endocarditis attacks sclerotic valves. Indeed, it is exceptional for normal segments to be affected. The recent investigations in experimental endocarditis by Orth[3] (which are confirmed by the beautiful demonstration of Prudden at this meeting) would indicate that the micrococci cannot lodge on the normal valve, but the slightest abrasion suffices to permit of their entrance. Although Ribbert[4] has been able to induce endocarditis by injecting cultures of the microörganisms without any previous lesion of the valves, particularly if the material was associated with rougher particles, these recent experiments support the experience of the post-mortem room that a damaged valve is the most likely to become the seat of ulcerative changes."

There follows a short discussion of the origin of this anomaly.

"*Origin.*—Whether the condition is the result of a foetal endocarditis or is an anomaly of development cannot be finally settled until we have fuller knowledge

[1] In case 4, a lad of twenty, in which rupture of a cerebral aneurism was the immediate cause of death, there was evidence of the connection of the aneurism with a previous embolic process, which might reasonably be associated with the valve lesion.

[2] British Medical Journal. Gulstonian Lectures, 1885, vol. i.

[3] Tageblatt der 58 Versammlung Deutscher Naturforscher zu Strassburg, 1885.

[4] Deutsche med. Wochenschrift, 1885, No. 42.

of the details of formation of the semilunar valves. The advocates of the inflammatory view urge that indications of the original separation invarably exist and that the valves as constantly present evidences of endocarditis. To this view Virchow has given the weight of his authority and has recently[1] stated that an examination of the question has convinced him that a majority of the cases show signs of a "secondary fusion of two cusps." This certainly may be so in some cases, but the following considerations lead, I think, to the conclusion that in many there is a faulty arrangement at the time of the development of the segments. . . ."

Osler at the very end of the paper, suggests that the anomalous condition of the aortic valves may be due to an error in their development.

"*Fourth.* If it turns out to be correct, as my cases indicate, that the affected valves are usually those behind which the coronary arteries are given off, this would point to some error associated especially with the development of these cusps. . . ."

He finally tabulates the pathological findings in his 18 cases and Nos. 9, 11, 13 and 18 are quoted from this table on account of their particular interest.

NO.	SEX AND AGE	CAUSE OF DEATH	STATE OF HEART	AORTIC VALVES	OTHER ORGANS	REMARKS
9	M 45 (?)	Ulcerative endocarditis	Much hypertrophied; weight 660 grms.	Coronary segments united; measure 4.5 cm. Sinuses of equal size. Raphé small. Shallow groove on ventricular surface at attachment of valve. Moderate sclerosis. Intercoronary segment covered with vegetation, and presents a perforation 2 by 1 cm.	Infarcts in spleen	In hospital four days. Malignant endocarditis
11	M 35 (?)	Ulcerative endocarditis	Much hypertrophy	Coronary segments united and sclerotic. Behind them a recent aneurism which projects into, and communicates with, left auricle. Vegetations on ventricular face. Intercoronary segment much thickened, and presents recent vegetations	Great enlargement of spleen; weight 500 grms.	Patient ill several months
13	M 38	Ulcerative endocarditis	Hypertrophy and dilatation	Coronary segments fused. Edge much thickened. Sinuses large, and the raphe scarcely visible. Intercoronary segment presents many recent vegetations, and is a little thickened	Extensive recent disease of mitral valve; infarcts	Marked typhoid symptoms
18	M 26	Ulcerative endocarditis, apoplexy	Hypertrophy of left ventricle	Fusion of coronary segments. Sclerotic changes. Vegetations on ventricular face. Perforation of valve. Vegetations on intercoronary cusp	Infarcts	Case simulated typhoid fever

[1] Virchow's Archiv, Bd. 103.

It seems probable that if not all, at least some, of these cases were examples of congenital bicuspid aortic valves, and if so this paper forms one of the earliest observations upon the occurrence of acute or subacute endocarditis in this condition. It was 37 years later that Lewis and Grant (6) published their well known article on the subject and 39 years before Maud Abbott (7) wrote extensively on inflammatory Processes in Cardio-vascular defects.

During the years immediately following the appearance of these papers, from which quotations have been so freely taken, Osler discussed the question of infectious endocarditis, according to Maud Abbott's "Bibliography of Osler," at medical meetings and in several unsigned editorials. For instance, he presented, some time between 1887 and 1889, two cases of ulcerative endocarditis (8) before the Path. Society of Philadelphia, one of which was supposed during life to be an instance of advanced "phthisis" in a young woman of 30 with heart disease.

There were, however, many other important matters to engage his attention. In 1889 he left Philadelphia to become Professor of Medicine at the Johns Hopkins Medical School and between 1890 and 1892 he was immersed in the absorbing work of writing his text book.

The first edition of the text book appeared in 1892. In it there is quite a long section on *Acute Endocarditis*. This is constructed very largely on the basis of his Gulstonian Lectures and his previous papers on the subject. There is no need to discuss this excellent and concise account of acute endocarditis as far as it was then known in detail, but it is noteworthy that at that time, he did not mention any specific bacteria as the causative agents of infectious endocarditis. It is important, on the other hand, to draw attention to what appears to be a growing realization that there was one type of case in which the course of the disease was surprisingly long. In the paragraph dealing with the "septic type" there occurs the following statement:

> "In a most remarkable sub-group of this type the disease may simulate a quotidian or tertian ague. The symptoms may develop in persons with chronic heart-disease without any external lesions. These cases may be much prolonged—for three or four months, or even longer, as in a case of Bristowe's. The existence in some of these instances of a previous genuine malaria has been a very puzzling circumstance."

And again in referring to the progress of acute endocarditis he states:

"The course of the disease is varied, depending largely upon the nature of the primary trouble. Except in the disease engrafted upon chronic valvulitis the course is rarely extended beyond five or six weeks. As already mentioned, there are instances in which the disease is prolonged for months."

In spite of his many exacting and varied duties, Osler evidently continued his studies of infectious endocarditis for in 1893, the very year that the Medical School opened, he published a paper in which he drew particular attention to the protracted course of the disease in two patients. Osler's description of these two cases, combined with his comments, leads one to believe that he was beginning to discern that there was or might be a particular type of infectious endocarditis, which, under the name of subacute bacterial endocarditis, is very familiar to us today.

The article starts, as usual, with references to Wilks, Bristowe and others, with a summary of the clinical features of the two cases.

THE CHRONIC INTERMITTENT FEVER OF ENDOCARDITIS. (9)

By William Osler, M.D., F.R.C.P. Lond.

Professor of Medicine in the Johns Hopkins University, and Physician-in-Chief to the Johns Hopkins Hosptial, Baltimore

(Practitioner, London 1893; *1:* 181–190)

"The type of endocarditis characterised by a protracted course and an irregular intermittent fever has been specially studied by Wilks, Bristowe, Coupland, and Lancereaux. In my Gulstonian Lectures (1885) its characters are thus described: The paroxysms may have the features of ague; the chill, hot stage, and sweating succeeding each other with regularity, and in the intervals there may be an entire absence of the fever. The quotidian type is the most common; the tertian has occasionally been described; and in rare instances two paroxysms have recurred within the twenty-four hours. The disease may be much prolonged, even to three or four months.

One of the first references I find to cases of this kind is in a footnote to one of Dr. Ormerod's Gulstonian Lectures,[1] in which a case of Dr. Bond, of Cambridge, is narrated—an instance of chronic valvular disease, with intermittent fever and diarrhoea, two paroxysms occurring in the day. The case lasted four months. In a remarkable case described by Dr. Wilks,[2] during a six or seven weeks' illness,

[1] *Medical Gazette*, 1851.

[2] *British Medical Journal*, 1868.

rigors recurred with such regularity that a tertain ague was suspected for a time, although the patient was known to be the subject of heart disease. In some instances, the existence of ague previously has rendered the condition much more puzzling. In several of Lancereaux's cases[3] the patients had had intermittent fever a short time before; so also with one of Leyden's cases.[4] But the most extraordinary case of the kind is recorded by Dr. Bristowe.[5] A patient had ague in October, with chills once or twice a day, in an illness of six weeks. After an interval of two or three weeks they recurred in the second week in December, and continued until December 23. She was well for a few days, and then the attacks recurred after sleeping in a cold bed, and persisted until her admission to hospital on February 12. For the four weeks previous to entrance, the attacks came every twelve hours regularly. A murmur was noticed; but the history of ague was so clear, and the attacks so characteristic, that a suspicion of malignant endocarditis was at first not entertained. It was only after the failure of quinine, and a variation in the character of the paroxysms, that a diagnosis was reached. In this case, the most protracted with which I am acquainted, the condition persisted for more than five months, and Dr. Bristowe has informed me that he regarded the case as one of ulcerative endocarditis from the outset.

I have recently had under observation a remarkable case in which the symptoms persisted for nearly ten months; and through the kindness of Dr. Mullin of Hamilton, Ontario, I am able to give the notes of a second case in which the disease continued for eleven months. The clinical features of these two cases may thus be summarised:

(1) Daily intermittent pyrexia for many months, the temperature rising to 102°.5 and 104°, occasionally preceded by a distinct rigor, more commonly by feelings of slight chilliness. Following the pyrexia there was more or less sweating.

(2) Progressive failure of strength, with varying intervals of improvement.

(3) Physical signs of cardiac disease—in the cases here reported an apex systolic murmur, with hypertrophy of the left heart.

(4) Development towards the close of the embolic symptoms more usually associated with ulcerative endocarditis, and cutaneous ecchymoses."

The first patient was a man of 43. Early in December, 1891, he suddenly fell ill with a chill and fever followed by malaise, fatigue, cough, pains in different parts of his body and loss of weight. The patient was under observation from March 15 to May 10. During this period he had irregular fever, signs of a lesion of the mitral valve, and pain and tenderness in the splenic region, though the spleen was

[3] *Gazette de Médecine*, 1862; *Archives Générales*, 1873.

[4] *Zeitschrift f. klin. Med.*, vol. iv. Berlin.

[5] *British Medical Journal*, 1881.

not palpable. When he was discharged from the Johns Hopkins Hospital the following final note was made.

". . . Repeated examinations showed no apparent change in the cardiac condition. The intense systolic murmur at the apex, obliterating the first sound, persisted. No increase could be determined in the area of cardiac dulness. The sounds in the aortic region remained clear. The patient left the hospital on May 10, and the history chart was headed "chronic vegetative endocarditis."

The subsequent history is interesting on account of the continuous fever and emaciation, the appearance of petechiae and the late urinary findings.

"For the subsequent history I am indebted to Dr. Block, who has sent the careful temperature chart kept by the nurse up to the time of the patient's death. From this it may be gathered that the temperature range throughout May and June was from 97° to 103°. In July the average was decidedly lower, and towards the end of the month he had several days when the temperature was almost normal. Early in July petechiae appeared, and several groups of these were noticed. On August 19 the temperature became normal, and remained so until the 24th; but the pulse was weak and he had free sweats. During the first week in September the temperature was usually sub-normal, and only reached 98° in the evening. The morning temperature was frequently 95°. There were profuse perspirations. From the 9th until his death on the 14th the temperature only once registered 98°, and for four days was continuously below 96°. He failed progressively, became extremely emaciated, had diarrhoea, and there were blood-corpuscles and blood-casts in the urine. The pulse was feeble, irregular, and intermittent. There were no brain symptoms, and he remained conscious until the last."

At autopsy there were enormous vegetations on the mitral valve, slight enlargement of the spleen with anaemic and softened infarcts, enlarged kidneys showing infarcts, and petechial hemorrhages over the peritoneum. No bacteriological examinations or cultures were made.

The description of the disease in this patient conforms very well to a case of subacute bacterial endocarditis, while in the second patient the clinical picture is even more characteristic, and therefore sections of the history and examination are quoted in full.

". . . The patient has generally enjoyed good health, but at twelve years of age she had an attack of rheumatism, apparently not severe, as she was in her room only one week, and not in bed all of the time. About four years before the onset of her last illness she had pain and slight swelling in one knee, was not confined to

bed, but wore a splint for a week. She has always been pale, and when at boarding school her teacher often suggested that iron would be of use. She, however, did not feel ill, and scarcely ever thought that she required medical treatment. At times, however, upon some sudden exertion she felt a stabbing pain in the region of the heart which never lasted long. The menses were always regular until the early part of the illness. . . . In February 1888, she caught cold when tobogganing, and had pain in the back part of the chest, but did not require to go to bed. In March she visited some friends at Niagara Falls, where she remained until July. Here her friends noticed that she looked miserable for some time before she spoke of being ill. The menses failed to appear, and she thought this was the reason why she did not feel so well as usual. She sometimes had attacks of faintness, which soon passed away on taking a stimulant. She became weaker, and had fever followed by night sweats; the fever came on in the afternoon. A physician was consulted, who said the heart was affected and that she required prolonged medical treatment and rest. She continued, however, to go about, and frequently took long walks, though on exertion she complained of being short of breath. She had fever and sweating at night, and was often so restless that she was obliged to leave her bed and recline on the sofa. . . . "

". . . . In the first week of July she came home, and was placed under my care. In the forenoon the temperature appeared normal, but every afternoon it rose to 102° or 103°. For a time she was thought to have typhoid fever, but no distinctive symptoms appeared. . . ."

". . . No local symptoms arose to account for the fever; pain was not complained of to any great extent; sometimes, for a few hours or half a day, there would be aching and pain in the hands and different joints, but these were always transient and at no time after she came home was there marked tenderness or swelling in any of the joints. When she reached home there was some swelling of the ankles and knees, but this soon passed away as she remained in bed. Not making any exertion she did not suffer from dyspnoea. There was a loud systolic murmur at the apex; and from the first the signs of hypertrophy showed that mitral disease had existed for some time. Before she came home it was noticed at the outset of the illness that small spots appeared on the hands and feet, also on arms and legs and face, that looked like "hives." These continued to appear; they were erythematous, some as small as a pea, others as large as a five-cent piece, with a white point in the centre. They often passed away in a few hours, and never lasted longer than the evening of the day on which they appeared. They were not numerous; sometimes they would appear near the tips of the fingers which for a short time became swollen. These spots were seen more or less throughout the illness, though more of them were noticed in the early part. . . ."

". . . A careful temperature record was kept in this case from July 17, 1888, until July 7, 1889. The type or fever was in each month remarkably uniform;

the morning record always at or below the normal point, and the evening record reaching 102°.5, 103°, and sometimes 104°. At intervals for a week or two the evening temperature did not fall below 100°."

"The *autopsy* showed moderate enlargement of the heart, due chiefly to hypertrophy and dilatation of the left ventricle. The aortic valves were normal; the mitral orifice readily admitted two fingers; the valve segments were thickened and presented numerous large vegetations, chiefly on the auricular surfaces, and extending from the base of the posterior segment to the wall of the left auricle. The chodeae tendineae were a little shortened and thickened, and many of them encrusted with the vegetations. The spleen and kidneys contained numerous infarcts in all states of change."

"The diagnosis of these protracted cases is often very difficult, and not unnaturally they are mistaken at the outset for malarial fever, particularly when daily chills occur. . . .

One very important observation in this second case was the presence of a generalized eruption which also occurred at times near the tips of the fingers. Both of these cases are referred to by Osler in a later paper as instances of "Chronic Infectious Endocarditis." He pointed out then that the eruption observed in the second case was the first instance of this particular sign, now known as "Osler's nodes," that had come to his attention. It was not, however, until 15 years had elapsed that this later communication appeared.

In the meantime he had been offered and had accepted the Regius Professorship of Medicine at Oxford. He left Baltimore to make his home in England in the spring of 1905.

An event took place the following year which has had great influence upon the development of clinical medicine, not only in England but in the world at large. It can best be described by quoting a page from Cushing's Life of Sir William Osler (3)—Vol. II, page 49.

"There was a movement on foot, about the time of Osler's transfer to England, fostered chiefly by Drs. Wilmot Herringham, A. E. Garrod (now Osler's successor), William Hale-White, H. D. Rolleston, J. Rose Bradford and Robert Hutchison, to start a new medical journal of a type rather different to any then being published in England; and, recognizing how great would be the value of his support, Osler was approached on the subject. To judge from contemporary letters, he had another project in mind and saw the chance of fusing his scheme with this other one. Accordingly, at the preliminary meeting held on May 23rd at Herringham's house, in the course of the discussion he casually remarked: "Why not form a National Association of Physicians first, and let the journal come to be its official

organ?"—adding that the Oxford Press might be prevailed upon to undertake the publication, though it was somewhat out of their line. The suggestion was warmly welcomed, and as an outcome of this informal gathering the Association of Physicians of Great Britain and Ireland, with the Quarterly Journal of Medicine as its official mouthpiece, came into being, and the Oxford University Press made its first venture into the field of medical publications. Though Osler never held an official position in the association he served for the following twelve years, until the time of his death, as one of the editors of the journal, and is said to have been "indefatigable in encouraging its growth, shaping its policies and smoothing out its difficulties."

The first meeting of the Association of Physicians of Great Britain and Ireland was held in London in the rooms of the Royal Medical and Chirurgical Society on May 23 and 24, 1907. At this meeting Osler presented a paper on "Multiple Hereditary Telangiectasis," which appeared subsequently in the first number of the "Quarterly Journal of Medicine," of which Osler had been appointed editor in chief. The second meeting of the Association opened in Edinburgh in June 1908 and it was at this meeting that Osler presented his work on "Chronic Infectious Endocarditis."

At this time Osler was familiar with the work of Harbitz and of Lehnhartz and though he refers to a case in which Horder had used vaccines, he does not mention the investigations of Schottmüller (10) on the differentiation of haemolytic streptococci from streptococcus viridans.

Osler's contribution to the subject was noteworthy. The paper is frequently quoted on account of the fact that, in it he described and emphasized one form of eruption which occurs in subacute bacterial endocarditis, now generally designated "Osler's nodes." But over and above this observation the communication has distinction, for he gives a clear and concise account of a condition which though recognized before this time even by Osler himself, had been ill defined. In this article a disease now very familiar as "subacute bacterial endocarditis" is presented as a definite clinical and pathological entity even though its origin cannot always be attributed to exactly the same variety of bacteria.

For these reasons several excerpts from this paper are quoted in full. It starts as usual with a definition, and with references to similar cases that had previously been reported. In this connection he makes the

statement that when he gave his Gulstonian Lectures he had not seen a case of this type, but one wonders in retrospect whether some of the cases of infectious endocarditis to which he refers in these lectures were not actually rather rapidly progressing instances of subacute bacterial endocarditis. This interpretation is certainly applicable to some of the cases described in his later communications, for it seems highly probable that cases 11; 13; and 18 in his paper on "The Bicuspid Condition of the Aortic Valves" (5) which appeared in 1886 were of this nature; and that the young woman whose illness he described at a meeting of the Pathological Society in Philadelphia about the year 1887 and printed in 1891 (8) might well have had subacute bacterial endocarditis. The following quotations have been selected as being particularly important.

CHRONIC INFECTIOUS ENDOCARDITIS

By William Osler[1] (11)

(Quarterly J. M. Jan. 1909; *2:* 219)

"An endocarditis with fever as its only symptom may be prolonged for weeks or months under many different circumstances. . . . That occasional instances were characterized by a very protracted course was noted by Wilks, Bristowe, Coupland, and Lanceraux. In my Gulstonian Lectures, 1885, I stated that this type had the following characteristics: the fever was irregular and intermittent, resembling ague; the cold, hot, and sweating stages might succeed each other with great regularity; in the intervals fever might be absent; two or three paroxysms could occur in the course of a day. In many of the instances the disease was prolonged to three or four months, and I give the notes of a case of Bristowe's in which the condition persisted for five months. The recurring chills usually led to the diagnosis of malaria and also gave rise to the opinion widely held, particularly by French writers, that ulcerative endocarditis could be caused by this disease. The cases to which I wish to call attention in this communication are of this chronic character, not marked specially by chills, but by a protracted fever, often not very high but from four to twelve months' duration. At the time of the deliver of the Gulstonian Lectures I had not seen a case of this type. In the past twenty years I have seen ten cases of this form, two of which I have already reported (Practitioner, 1893). I have put them together in tabular form to indicate their main features.

Following these opening paragraphs Osler proceeds to enumerate the types of bacteria which had been found in association with infec-

[1] Read at the Association of Physicians of Great Britain and Ireland, Edinburgh, June 12, 1908."

tious endocarditis and mentions specifically "The pneumococcic, the gonococcic and the streptococcic forms." After referring to the frequency with which patients suffering from the "chronic" type of disease give a history of old rheumatic lesions of the heart valves he describes the course of the fever which is such a characteristic feature of the disease.

"...Once established the fever becomes the dominant, and for many months may be the only, symptom. This is the most striking peculiarity of the cases. Week after week, month after month, the daily rise of one and a half or two degrees may be the only indication there is of an existing mischief. In Case 1, in which the fever lasted for thirteen months, the patient's sister, a trained nurse, had decorated the room with yards of the temperature charts; fever with an occasional sweat were the only symptoms. The appetite remained good and she lost very little weight. There were no embolic features and from month to month there were few, if any, changes in the cardiac condition."

The clinical signs referable to the cardiac lesions were matters of some significance as the following paragraph illustrates.

"... One of the most striking circumstances is the very slight change in the character of the heart murmur in spite of the fact of most extensive vegetations and alterations in the valves. Thus in the case of Dr. R. T., with the condition of whose heart I had been familiar for fourteen years, the comparison between my first examination in 1889 and that in 1893 showed very little change beyond the slightly greater dislocation outwards of the apex beat. In several of the cases the absence of any change in the character of the organ were urged strongly against the existence of endocarditis. It is rather remarkable, considering the anatomical changes, that so little alteration may occur in the physical signs. ..."

After a note concerning the embolic complications he goes on to describe the celebrated "Osler nodes."

"... One of the most interesting features of the disease and one to which very little attention has been paid is the occurrence of ephemeral spots of a painful nodular erythema, chiefly in the skin of the hands and feet, the "nodosités cutanées éphémerés" of the French. My attention was first called to these in the patient of Dr. Mullen of Hamilton, whose description is admirable: "The spots came out at intervals as small swollen areas, some the size of a pea, others a centimetre and a half in diameter, raised, red, with a whitish point in the centre. I have known them to pass away in a few hours, but more commonly they last for a day, or even longer. The commonest situation is near the tip of the finger, which may be slightly swollen." Spots of this character occurred in seven of the cases and in

three at least they were of importance in determining the diagnosis. Thus in the case of Dr. Carroll, the well-known American Army Surgeon, the collaborator with Dr. Reid in the brilliant work upon yellow fever, the presence of these spots appeared to me to clinch the diagnosis. They are not beneath but in the skin and they are not unlike an ordinary wheal of urticaria. In one case they were present in the skin of the flank. I have never seen them haemorrhagic, but always erythematous, sometimes of a very vivid pink hue, with a slightly opaque centre."

This is followed by a discussion concerning the difficulties of diagnosis with a statement regarding the most helpful signs and symptoms that may serve as guides.

"... By far the most suggestive features are: (1) a knowledge of the existence of an old valve lesion. This was present in every one of my series. (2) The occurrence of embolic features, sudden swelling of the spleen, with friction in the left flank, sudden attack of haematuria, embolism of the retinal arteries, hemiplegia or the blocking of a vessel in one of the limbs. (3) The onset of special skin symptoms, purpura, and more particularly the painful erythematous nodules to which I have referred. Present in seven of the ten cases, these are of definite diagnostic import. They are in all probability caused by minute emboli. (4) The progressive cardiac changes, the gradual increase in the dilatation of the heart, the marked change in the character of a mitral murmur, the onset of a loud rasping tricuspid murmur, or the development under observation of an aortic diastolic bruit. With carefully made blood-cultures one should now be able to determine the presence of the septicaemia. This was easily done in three of my more recent cases. ...The blood-cultures and the presence of the painful erythematous nodules and the occurrence of embolism furnish the most important aids."

There follows a short paragraph on the pathological lesions, and then an account of the results of bacteriological examinations of the blood in these patients.

"... The organisms responsible for this condition have been carefully studied. In my series cultures were made in six cases. In three they were negative. In two streptococci were present, in one a staphylococcus. While, as a rule, this condition is much more commonly caused by the streptococcus other organisms may be present. Thus Fraenkel has reported one instance of a pneumococcus endocarditis persisting for nearly six months (Deutsche med. Woch., 1900). Of sixteen cases of this chronic form, the clinical course of which extended from four to eight months, Harbitz (Deutsche med. Woch., 1899) found pneumococci in four, streptococci in nine, and in eight other micro-organisms. Lenhartz (Deutsche med. Woch., 1901), who has reported sixteen cases with a duration of from three to seven months, found staphylococci and streptococci the common organisms, the

penumococcus once and the gonococcus once. In the majority of cases it seems to be a mild streptococcus infection, possibly by a special form. Possibly in some instances there may be a special resistance on the part of the host, but these are points which must be settled by future investigations. These are cases in which the possibility of successful vaccine treatment should be considered. It was tried in two cases of my series, but in both rather late, and in neither did it seem to have special influence. Horder has treated a case of this chronic type with a vaccine prepared from the patient's organism, but without success. The results in the acute forms are discussed by him in the Practitioner, May, 1908. Abstracts of the cases are here given."

The article ends with a detailed account of each one of the 10 cases, two of which had been previously reported in 1893. A table showing the essential data in each case is appended and this appears below.

This paper by Osler appeared in the January 1909 number of The Quarterly Journal of Medicine, and in the April number of the same year, Horder published his article entitled, "Infectious Endocarditis" (12). In this article Horder states that he was stimulated to prepare the material which he was collecting for publication upon hearing Osler's presentation at the second meeting of the Association of Physicians of Great Britain and Ireland.

The analysis which Horder made of the 150 cases, with the numerous, excellent illustrations of pathological lesions was an important contribution to the subject. He noted the fairly frequent association of infective endocarditis with congenital cardiac lesions, quoting illustrative cases, drew attention to mycotic aneurysms, and tabulated the incidence of involvement of the different heart valves. With Andrewes he had previously reported the bacteriological findings in blood cultures from a few cases, but in this paper he lists the results obtained between 1905 and 1908 in 32 cases. In 19 a streptococcus was obtained, in 5 B. influenza, in 3 the pneumococcus, in 1 a gonococcus and in 1, staphylococcus albus. He emphasizes the frequency with which streptococci are responsible for the endocarditis, and states that, in 100 cases examined at autopsy at St. Bartholomew's Hospital between 1901 and 1908, this organism was cultured in 62 instances. He also points out that the commonest forms of streptococci recovered in culture were not the S. pyogenes but less virulent varieties termed "salivarius," "anginosus" or "faecalis"; and that these organisms might be present in enormous numbers in the circulating blood.

Summary of Ten Cases of Chronic Infectious Endocarditis

NO.	NAME	AGE	DATE	FORMER RHEUMATIC FEVER	OLD VALVE LESION	EARLY SYMPTOMS	TYPE OF FEVER	SKIN SYMPTOMS	EMBOLISM	HEART LESIONS	DURATION
											months
1	J. M.	28	July, 1888	Yes	Mitral	Fever	Remittent and intermittent	Painful nodular erythema	None	Mitral endocarditis	13
2	T. B.	43	March, 1892	No	Mitral	Chills and fever	Remittent	Purpura	None	Mitral endocarditis	10
3	Florence D.	21	March, 1899	Yes	Mitral	Chills and fever	Remittent	Painful nodular erythema	Brain	No p.m.	7
4	Mary B.	19	June, 1890	Yes	Mitral	Chills and fever	Remittent	Painful nodular erythema	Brain	No p. m.	5
5	R. B.	53	May, 1902	No	Aortic	Chills and fever	Remittent with chills	—	None	No p.m.	4
6	Dr. B. T.	33	Sept., 1902	No	Aortic	Arthritis, chills, fever	Intermittent and remittent	Painful nodular erythema	None	No p.m.	8
7	Dr. R. T.	53	Feb., 1903	Yes	Mitral	Fever and sweats	Remittent	Painful nodular erythema	Retina, spleen, kidney	Mitral, aortic and tricuspid endocarditis	8
8	R. W.	36	Nov., 1906	Yes	Mitral	Chills and anaemia	Remittent	Purpura	None	No p.m.	6
9	Dr. C.	52	May, 1907	No	Mitral	Fever	Remittent	Painful nodular erythema	Brain	No p.m.	7
10	Alice A.	20	Jan., 1908	Yes	Mitral	Fever	Remittent	Painful nodular erythema	None	No p.m.	7

He then proceeds to divide the cases of infective endocarditis into 5 types. (1) Latent infective endocarditis; (2) Fulminating infective endocarditis; (3) Acute infective endocarditis and (4) Subacute infective endocarditis; this, the fourth being the commonest and occurring in 88 of the 150 cases. Finally No. 5, chronic infective endocarditis accounted for 18 of the 150 cases. Thus over 70% of the cases belonged to the subacute and chronic groups.

He then discusses the symptoms and signs of the disease, and points out in particular the occurence of embolism, the frequency of splenic enlargement, the presence of hemorrhagic renal lesions producing the "flea bitten" kidney, the varieties of skin eruption encountered with the diagnostic significance of petechiae, which he found early about the neck and upper chest. He also alludes to the nodes described by Osler.

He makes reference to the retinal lesions, and notes that they may be overlooked, for, like petechiae in the skin, they may be transient.

Some space is devoted to the types of fever encountered, and to the other symptoms which are now familiar.

In the section devoted to prophylaxis and treatment, he suggests that "Oral Sepsis" should receive careful attention, for as he states "Reference has been made to the undoubted fact that the source of the infecting agent in most cases is the mouth or intestine."

In relation to the treatment of this disease Horder used a long list of drugs without effect, anti-streptococcus serum proved useless; and 12 cases treated by vaccines, all died. He concludes that the disease is almost uniformly fatal. Some years later, Horder elaborated this entire subject in his Lumlian Lectures (13).

Though individual instances of subacute or chronic cases of bacterial endocarditis had been reported before the work of Osler, it is fair to say that his contributions together with the paper by Horder established without question the existence of a particular group of infective endocarditides, which since then have been the subject of the most extensive investigations.

The last published communication that Osler made upon infective endocarditis appears to be the report of a clinic conducted at the Radcliffe Infirmary on October 24, 1911. This paper seems rarely to be quoted. It is as follows:

CHRONIC INFECTIOUS ENDOCARDITIS, WITH AN EARLY HISTORY LIKE SPLENIC ANEMIA (14)

By Sir William Osler, Bart; M.D., of Oxford

Regius Professor of Medicine, Oxford University

"Clinical Remarks at the Radcliffe Infirmary" October 24, 1911

(Interstate Med. J. 1912; 19; 103. St. Louis, Mo.)

The subject for this clinic was a man of 33 who was sent into the wards in May by Dr. Waters with purpura, anemia and a greatly enlarged spleen. He had fever. The patient was thought to have splenic anemia, but in August he developed a well marked aortic systolic murmur and later a tender, painful swelling in the left groin which was considered to be an aneurysm. Osler then says,

"These features, of course, put an entirely different construction on the case' and it was evident that he had an infectious endocarditis. Cultures were made from the blood by Dr. Gibson, from which have grown a streptococcus which has the character of the form described by Libman in connection with these cases. I must say that this sequence of events was quite outside my experience, but there are one or two similar cases in the literature. Only the other day Dr. Parkes Weber, into whose clinical net come all sorts of peculiar and instructive cases, sent me a paper in which is described a case of malignant endocarditis, the early features of which resemble those of splenic anemia.*

After describing the autopsy at which extensive vegetations were found on the aortic valves and drawing attention again to the prominent enlargement of the spleen, he concludes by enumerating the important features of this type of infective endocarditis. They are listed as:

"1. Chronicity
2. Latency
3. Fever of the so called septic type
4. Embolic attacks
5. Ephemeral Cutaneous nodes
6. Blood cultures
7. Lastly the endocarditis is pathologically unlike the ordinary ulcerative form"

---

* British Journal of Dermatology. February 1910.

Though some enlargement of the spleen is common in subacute bacterial endocarditis, it is only the occasional case, and usually during the bacteria free stage, as Libman (15) has emphasized, that this organ attains very great size. The case reported by Osler is one of the earliest on record, in which great enlargement of the spleen was combined with bacteraemia.

There is no intention of reviewing the vast literature on subacute or chronic bacterial endocarditis, for this has been done recently by Libman, (15) who gives 226 references to papers on this subject. The aim of this study is to follow through Osler's contributions, his gradual realization that there was a form of infective endocarditis that could be distinguished by its symptoms, by its signs and by the duration of the illness from the acute variety of the disease. This concept culminated in his paper published in 1909; and was almost immediately substantiated by the publication of Horder's elaborate investigations. During the next year Schottmüller (16) added still further evidence to support this conclusion, by his description of cases of what he termed "Endocarditis Lenta." These, he discovered, were caused by streptococcus viridans. The disease soon became familiar in this country through the work of Libman (17, 18, 19) who, in addition to other observations reported the occurrence of cases in a so called "bacteriae free stage." Loehlein (20) described in detail the form of hemorrhagic nephritis that is related to subacute bacterial endocarditis. Baehr (21, 22) made careful studies of the renal lesions in subacute bacterial endocarditis and found that a diffuse glomerulur nephritis was most apt to occur in those patients who died in the bacteria free stage of the disease.

The literature on subacute bacterial endocarditis accumulated so rapidly that Debré (23) in 1919 collected sufficient material for a review of the subject which was elaborated still further by Blumer (24) in 1923, whose article forms the basis of our information on the subject up to that time. Libman stated in 1918 that he had seen 300 cases.

It seems surprising that up to this time almost no mention had been made in the general literature of the clubbed fingers that so often appear during the course of the disease. As early as 1912 Major (25) mentions this sign which was recorded in the histories of 3 of 6 cases of

subacute bacterial endocarditis amongst 15 probable cases occurring in The Johns Hopkins Hospital. He also noted that though patients might have negative blood cultures during life, culture from the vegetations on the heart valves at autopsy, yielded streptococci. Cotton (26) had noted the presence of clubbed fingers in 1920 and published a more elaborate study of this condition in his cases of subacute bacterial endocarditis in 1922 (27). In a survey of 721 cases of valvular disease occurring in Lewis' Clinic he found that 63 patients had clubbing of the fingers. Of these 63 cases, 44 or 70% had the signs and symptoms of chronic infective endocarditis. Sometime later Blumer (28) though he had omitted to mention the subject in his review, reported similar cases and in addition described the splinter-like hemorrhages beneath the finger nails.

Osler's early observations on the occurrence of infectious endocarditis in patients with malformed aortic valves, most of which he considered to be congenital defects, have already been quoted in some detail, but his paper seems to have attracted little attention. That the matter is one of importance has been pointed out by Lewis and Grant (29, 30) in their classical papers on the subject. Indeed as was shown by Abbot (7) somewhat later, other congenital malformations of the heart such as patent ductus arteriosus, as was recorded by Robinson (31) in 1905, and patent interventricular septum, may form a nidus for engrafted bacterial infections. These papers are of considerable significance in relation to the general conclusions that subacute bacterial endocarditis does not usually affect the aortic valves in syphilitic aortitis (32) although as Grant (33) has found in his elaborate analysis of 1000 men suffering from heart disease, subacute bacterial endocarditis occurred in non-syphilitic disease of the aortic valves much more frequently than in any other group, a fact which also appears in Osler's papers. In the entire lot of 1000 men, subacute bacterial endocarditis on one or another valve, was present or developed during the 10 year period in 12%.

As will be pointed out later, the realization that subacute bacterial endocarditis may be engrafted upon congenital cardiac defects is significant in relations to the introduction of operative measures in an effort to cure those cases in which a patent ductus arteriosus is affected.

It is desirable to draw particular attention to Thayer's (34, 35) ex-

tensive investigations upon infective endocarditis since these come as a sequel, so to speak, at The Johns Hopkins Hospital, to the earlier studies of Osler; and as Osler's experiences in Montreal formed the basis for his Gulstonion Lectures, so Thayer's review of the cases in Baltimore furnished the material for his Gibson Lectures in Edinburgh in 1930. Thayer was able to collect and analyse the records of 306 carefully studied cases of infective endocarditis that had been admitted to The Johns Hopkins Hospital during a period of 40 years, or which he had seen in private practice. To these he added 232 cases recorded in the literature, making a total of 538 cases of the disease. He classified his cases according to the etiology, and defines subacute streptococcal endocarditis as one phase of the entire group in which streptococci of all varieties were the etiological agents. This organism he found was the cause of infective endocarditis in 62.5% of the 536 recorded cases. He pointed out that B. influenza always, and B. hemolytic streptococci sometimes, gave rise to a clinical picture indistinguishable from that produced by the different strains of streptococcus viridans which organism, with these exceptions, was invariably the cause of the subacute or chronic form of bacterial endocarditis. In this latter group, pericarditis is rare compared to its incidence in acute rheumatic fever and pneumococcus endocarditis. He further made the observation that of 84 cases of the subacute variety of streptococcal endocarditis in which notes as to the condition of the teeth had been made, peridental infection was present in 54; and that in several patients the onset of the malady could be directly traced to an operation on the facial sinuses, the tonsils or the extraction of teeth.

These latter statements are in accord with previous references to the connection of oral sepsis as a portal of entry for streptococci in subacute bacterial endocarditis, a relationship which is now known to be of great frequency and importance. This was emphasized by Weiss (36) who suggested from his study of 364 cases that foci of infection due to streptococci in the mouth and upper respiratory tract were common sources of entry for these organisms in this disease. He reported 10 cases in which a history of tonsillectomy or the extraction of a tooth closely antedated the onset of symptoms. These suspicions received unquestionable support through the investigations of OKell and Elliott (37). These authors found that blood cultures from 138 patients un-

dergoing operation for extraction of teeth made within 5 minutes after extraction gave a growth of streptococcus viridans in 84 instances, or in 60.9%. Of 40 cases in which there was marked gum disease, necessitating multiple extractions, there were positive cultures in 30, or 75%, and in 38 patients even without detectable gum disease, extraction of one or more teeth resulted in positive blood cultures in 12 or over 31%. The implication of these investigations is obvious. They have been confirmed (38) and have formed the basis for the necessity of prophylactic treatment in all such operative proceedures, but particularly in patients with valvular heart disease. Though the sulfonamides, as will be pointed out later have been of little value, penicillin has proven very effective.

Ever since subacute bacterial endocarditis was established as a clinical entity, every conceivable method of treatment that could be devised has been employed. Only recently has any substantial benefit been accomplished. Thus White (39) states that there was only one recovery in 250 well authenticated cases treated by every means known in the Boston Hospitals during 15 years prior to 1939. Though the disease has been considered almost uniformly fatal, a few spontaneous recoveries have been reported (40). The percentage of such recoveries calculated from the reports of long series has been given as from 1% to 3% of cases (41). Libman (42) reported 4 spontaneous recoveries in a series of 150 cases, but Lichtman and Bierman (43) who collected the data on 634 cases found only 6 recoveries or an incidence of 1%.

When the sulfonamides were introduced for the treatment of infections due especially to certain gram positive bacteria, great hopes were entertained that one or another of these drugs would prove efficacious in the treatment of subacute bacterial endocarditis due to streptococcus viridans. During the first few years of these trials, cases were reported in which there was, for a time, considerable improvement, but relapse was generally the rule; and it soon became evident, that, even with such adjuvants as hirudin, introduced by Kelson and White (44, 45), or hyperthermia, the total mortality was not very greatly reduced. For instance Lichtman and Bierman (43) give in their collected statistics a recovery rate in 198 cases of 6% for chemotherapy alone, and in 88 cases a recovery rate of 16% for chemotherapy combined with hirudin or hyperthermia in some form. In a review

of these forms of chemotherapy, Hunter (46) states that "at best 10% of recoveries were reported with sulfonamides alone, although, in some small series, 25% cures occurred when fever therapy was employed in addition."

During this period of chemotherapy an entirely new and different approach to the problem of therapy was introduced. This consisted in the ligation, by operative proceedures, of the ductus arteriosus in patients in whom this structure was the seat of subacute bacterial endocarditis. Touroff (47) who was active in this field, reported in 1940 what seemed to be a cure of 5 cases by this method. The next year he published (48) the results which he had obtained in 11 cases. Two patients died of operative hemorrhage. Of the nine survivors 6 recovered from the infection without benefit of chemotherapy. Of the 3 successful results, at least 2 patients presented evidence of involvement of the valves of the heart as well as of the patent ductus arteriosus.

In this connection reference must be made to the remarkable case described much earlier by Hamman and Rienhoff (49) in which streptococcus viridans septicaemia was cured by the resection of an infected arterio-venous aneurysm between the external iliac artery and vein.

What appears to be, up to the present time, the final chapter in the treatment of subacute bacterial endocarditis, came with the introduction of penicillin. This antibiotic has proven to be highly effective. The recent papers by Hunter(46); by Favour, Janeway and their associates (50), and by Herring and Davis (51) furnish information concerning various aspects of this important subject. Hunter's results were highly successful. Of 49 patients treated at the Presbyterian Hospital in New York, 90% were cured of their infection. As 4 of these patients died later of causes unrelated to the infection, the actual recoveries amounted to 83%. He makes the point that enormous amounts of penicillin are required to control the infection when this is caused by a relatively resistant strain of streptococci. In one patient, 20,000,000.00 units a day for 16 days was required and in another patient 10,000,000.00 units in constant drip for 3 weeks. Favour et al. (50) record the results of treatment by penicillin in 17 cases, in 11 of which the infection was cured or arrested, and Herring and Davis (51) record 18 cases in which the infection was arrested in 13. Of

the 18 patients only 10 were alive and well, however, after one year or more. The figures given for these three series afford some idea of the differences in the number of "cures" reported by various observers. Libman (15) states that the administration of penicillin to 103 cases, reported by 6 groups of workers resulted in the cure of infection in 107 or 81.7%. Herring and Davis (51) conclude from an analysis of the literature that an average of 75% of cases have been cured by penicillin therapy.

The most comprehensive study of this entire problem has been made by Anderson and Keefer (52) who have analysed elaborately in their monograph the results of treatment by penicillin in 690 cases of Bacterial Endocarditis. Non-heamolytic streptococci were the cause of endocarditis in 457 of these patients. Arrest of the infection occurred in 282 instances or in 62% of cases. Temporary improvement occurred in 25 patients or 5.3%; the result was indeterminate in 3 or 0.7% and 147 or 32% died during treatment. The greatest number of deaths in the fatal group were due to primary infection, congestive heart failure and to cerebral embolism in order of frequency. These three conditions were responsible for death in 108 of the 147 fatalities.

It would involve an extensive discussion of the methods of administration of penicillin and the relative resistance of the infecting organism among other factors to explain why the infection was not controlled in some cases, a problem that is beyond the scope of this paper; but it is necessary to add a word concerning the fatal outcome in those patients in whom it has been shown by autopsy that the infection itself has healed completely. There appear to be at least 2 conditions that account for these deaths following recovery from the infection. One of these, as pointed out by Bloomfield (52), and considered recently by Rapoport and Ellis (53), is progressive and uncontrollable cardiac failure, due supposedly to extensive injury or destruction of one or another of the heart valves; the other is cerebral embolus. Both of these complications have been frequently noted by many writers and both at the present time appear usually to be unpredictable and unfortunately unavoidable. It has been suggested, however, that if treatment by penicillin is instituted early in the disease the danger of subsequent cardiac failure may be lessened.

It rarely happens that one can trace through scarcely more than

half a century the development of knowledge concerning a disease from its earliest definition through its recognition as a comparatively common clinical entity, which was almost uniformly fatal, to the discovery of its etiological agent or agents, with subsequent means of cure in at least 75% of cases. But so it is with subacute bacterial endocarditis. This is a disease with which Osler's name will always be associated, for his acute observations went far in establishing it as a clinical entity, and in stimulating interest in a condition that was difficult of diagnosis and practically resistant to all forms of treatment during his life time.

The sequence of events leading finally to an effective treatment of the disease, are illustrative of the astonishing advances that have been made in many fields of medicine during the last quarter of a century.

BIBLIOGRAPHY

(1) Osler, W.: Infectious (so called ulcerative) Endocarditis. Arch. Med., 1881; **5:** 44.

(2) Osler, W.: On Some Points in the Etiology and Pathology of Ulcerative Endocarditis. Trans. Internat. Med. Cong. London, 1881; **1:** 341.

(3) Cushing, H.: The Life of Sir William Osler. Oxford-Clarendon Press, 1925.

(4) Osler, W.: The Gulstonian Lectures on Malignant Endocarditis. Brit. Med. J. 1885; **i:** 467, 522, 577.

(5) Osler, W.: The Bicuspid Condition of the Aortic Valves. Trans. Ass. Am. Phys., 1886; **i:** 185–192.

(6) Lewis, T., and Grant, R. T.: Observations relating to Subacute Infective Endocarditis. Heart, 1923; **10:** 21.

(7) Abbott, M. E.: On the Incidence of Bacterial Inflammatory Processes in Cardio-Vascular Defects and on Malformed Semilunar Cusps. Ann. Clin. Med., 1925; **4:** 189.

(8) Osler, W.: Two Cases of Ulcerative Endocarditis. Trans. of Path. Soc., Philadelphia, 1891; **14:** 123.

(9) Osler, W.: The Chronic Intermittent Fever of Endocarditis. Practitioner, 1893; **i:** 181.

(10) Schottmüller, H.: Die Artunterscheidung der für den Menschen Pathogenen Streptokokken durch Blutagar. Münch. Med. Wochscft., 1903; **50:** 849.

(11) Osler, W.: Chronic Infectious Endocarditis. Quart. J. of Med., 1909; **2:** 219.

(12) Horder, T. J.: Infectious Endocarditis, with an Analysis of 150 Cases and with Special Reference to the Chronic Form of the Disease. Quart. J. of Med., 1909; **2:** 289.

(13) HORDER, T. J.: Lumlian Lectures on Endocarditis. Brit. Med. J., 1926; **i:** 603, 641, 733.

(14) OSLER, SIR WILLIAM: Chronic Infectious Endocarditis, with an Early History like Splenic Anemia. Interstate Med. J., 1912; **19:** 103.

(15) LIBMAN, E.: Subacute Bacterial Endocarditis. Oxford Medicine, 1947; *Vol. 2:* 347.

(16) SCHOLLMÜLLER, H.: Endocarditis Lenta; Zugleich ein Beitrag Zur Artunterscheidung der Pathogenen Streptokokken. Münch. Med. Wchnsehr., 1910; **57:** 617.

(17) LIBMAN, E., AND CELLER: Subacute Infective Endocarditis. Am. J. of Med. Sc., 1910; **140:** 516.

(18) LIBMAN, E.: A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, with Particular Reference to Healing or Healed Lesions; with Clinical Notes. Am. J. of Med. Sc., 1912; **144:** 313.

(19) LIBMAN, E.: The Clinical Features of Cases of Subacute Bacterial Endocarditis that have Spontaneously Become Bacteria-Free. Trans. Ass. Am. Phys., 1913; **28:** 309. Am. J. Med. Sc., 1913; **146:** 625.

(20) LOEHLEIN, M.: Über hamorrhagishe Nieren Affektionen Bei Chronisher Ulzeröser Endocarditis. Med. Klinik, 1910; **6:** 375.

(21) BAEHR, G.: Glomerular Lesions of Subacute Bacterial Endocarditis. Am. J. of Med. Sc., 1912; **144:** 327. J. Exp. Med., 1912; **15:** 330.

(22) BAEHR, G.: The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis. Arch. of Int. Med., 1921; **27:** 262.

(23) DEBRÉ, R.: L'endocardite Maligne a Forme Lente. Revue de Med., Paris, 1919; **36:** 346, 438, 509.

(24) BLUMER, G.: Subacute Bacterial Endocarditis. Medicine, 1923; **2:** 105.

(25) MAJOR, R. H.: Clinical and Bacteriological Studies on Endocarditis Lenta. J. H. H. Bull., 1912; **23:** 326.

(26) COTTON, T. F.: Subacute Infective Endocarditis. Brit. M. J., 1920; **2:** 851.

(27) COTTON, T. F.: Clubbed Fingers as a Sign of Subacute Bacterial Endocarditis. Heart, 1922; **9:** 347.

(28) BLUMER, G.: Digital Manifestations of Subacute Bacterial Endocarditis. Am. Ht. J., 1926; **i:** 257.

(29) LEWIS, T., AND GRANT, R. T.: Observations Relating to Subacute Infective Endocarditis. Heart, 1923; **10:** 21.

(30) GRANT, R. T.: Aortic Lesions of Subacute Infective Endocarditis. Heart, 1924; **11:** 9.

(31) ROBINSON, G. C.: The Relations Between Congenital Malformations of the Heart and Acute Endocarditis and the Report of Two Cases. Bull. Ayer Clin. Lab., 1905; **2:** 45.

(32) MARTIN, H. E., AND ADAMS, W. L., JR.: Bacterial Endocarditis Superimposed on Syphilitic Aortitis Valvulitis. A Clinicopathological Study with 5 Case Reports. Am. Ht. J., 1938; **16:** 714.

KOLEYSKY, S.: Syphilitic Cardiovascular Disease and Bacterial Endocarditis. Am. Ht. J., 1942; **23:** 208.

(33) GRANT, R. T.: After Histories for Ten Years of a Thousand Men Suffering from Heart Disease. A Study in Prognosis. Heart, 1933; **16:** 275.

(34) THAYER, W. S.: Studies on Bacterial (Infective) Endocarditis. J. H. H. Reports, 1926; **22:** 1.

(35) THAYER, W. S.: Bacterial or Infective Endocarditis. Edinburgh Med. J., 1931, April, p. 237.

(36) WEISS, H.: Relation of Portals of Entry to Subacute Bacterial Endocarditis. Arch. Int. Med., 1934; **54:** 710.

(37) OKELL, C. C., AND ELLIOTT, S. D.: Bacteraemia and Oral Sepsis with Special Reference to the Aetiology of Subacute Bacterial Endocarditis. Lancet, 1935; **2:** 869.

(38) PRESSMAN, R. S., AND BENDER, I. B.: Effect of Sulfonamide Compounds on Transient Bacteraemia Following Extraction of Teeth. Arch. Int. Med., 1944, **74:** 346.

(39) WHITE, P. D.: Heart Disease, p. 364; 3-Ed. 1946. Macmillan & Co., N. Y.

(40) LIBMAN, E.: A Study of the Endocardial Lesions of Subacute Bacterial Endocarditis, with Particular Reference to Healing or Healed Lesions; with Clinical Notes. Am. J. Med. Sc., 1912; **144:** 313.

(41) SMITH, C., SAULS, H. C., AND STONE, C. F.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans. J. A. M. A., 1942; **119:** 478.

(42) LIBMAN, E.: A Consideration of the Prognosis in Subacute Bacterial Endocarditis. Am. Ht. J., 1925; **i:** 25.

(43) LICHTMAN, S. S., AND BIERMAN, W.: The Treatment of Subacute Bacterial Endocarditis:—Present Status. J. A. M. A., 1941; **116:** 286.

(44) KELSON, S. R., AND WHITE, P. D.: A New Method of Treatment of Bacterial Endocarditis. J. A. M. A., 1939; **113:** 1700.

(45) LEACH, C. E., FAULKNER, J. M., DUNCAN, C. N., MCGINN, S., PORTER, R. R. AND WHITE, P. D.: Chemotherapy and Heparin in Subacute Bacterial Endocarditis. J. A. M. A., 1941; **117:** 1345.

(46) HUNTER, T. H.: The Treatment of Subacute Bacterial Endocarditis with Antibiotics. Am. J. of Med., 1946; **i:** 83.

(47) TOUROFF, A. S. W.: The Rationale of Operative Treatment of Subacute Bacterial Endarteritis Superimposed on Patent Ductus Arteriosus. Am. Ht. J., 1942; **23:** 847.

(48) TOUROFF, A. S. W.: Results of Surgical Treatment of Patency of the Ductus Arteriosus Complicated by Subacute Bacterial Endarteritis. Am. Ht. J., 1943; **25:** 187.

(49) HAMMAN, L., AND RIENHOFF, W. F., JR.: Subacute Streptococcus Viridans Septicaemia: Cured by Excision of an Arteriovenous Aneurysm of External Iliac Artery and Vein. J. H. H. Bull., 1935; **57:** 219.

(50) FAVOUR, C. B., JANEWAY, C. A., GIBSON, J. G., JR., AND LEVINE, S. A.:

Progress in the Treatment of Subacute Bacterial Endocarditis. New. Eng. J. of Med., 1946; **234:** 71.

(51) HERRING, A. C., AND DAVIS, W. A.: Penicillin Treatment of Subacute Bacterial Endocarditis—Reports of Eighteen Consecutive Cases. J. A. M. A., 1948; **138:** 726.

(52) ANDERSON, D. G., AND KEEFER, B. S.: The Therapeutic Value of Penicillin. A study of 10,000 cases—1948; J. W. Edwards, Ann Arbor, Michigan.

(53) BLOOMFIELD, A. L., ARMSTRONG, C. D., AND KIRBY, W. M. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin. J. of Clin. Inv., 1945; **24:** 251.

(54) RAPOPORT, B., AND ELLIS, L. B.: The Effect of Subacute Bacterial Endocarditis on the Course of the Underlying Heart Disease. New Eng. J. of Med., 1948; **239:** 951.

THE CLINICAL COURSE OF DISSEMINATED LUPUS ERYTHEMATOSUS

An Evaluation of Osler's Contributions

PHILIP A. TUMULTY and A. McGEHEE HARVEY

From the Department of Medicine, Johns Hopkins University, Baltimore

The subject of ulcerative endocarditis formed the thesis of Dr. Osler's Gulstonian Lectures in 1885. He began them as follows: "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point and to ascertain in what direction we may look for fruitful investigations in the future."

In such spirit we have undertaken this study of lupus erythematosus disseminatus, a disease to which Dr. Osler contributed such brilliant thought in a series of articles on "The Visceral Complications of Erythema Exudativum Multiforme," published between 1895 and 1903 (1–3).

None of Osler's cases was studied by morphological techniques, and some may not have had disseminated lupus erythematosus. Perhaps his emphasis on the prominence of abdominal symptoms has not been borne out by subsequent experience. However, it was Osler who first emphasized the fundamental concept that the alterations occurring in the skin of patients with this disease had their counterpart in the internal organs. The clinical genius of Dr. Osler could not be better exemplified than by the following description of the visceral complications of erythema exudativum multiforme which he wrote in his first article on this subject published in December, 1895, at a time when there was no knowledge of the pathological changes in this disease:

> "By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions—hyperemia, edema, and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastro-intestinal crises, endocarditis, pericarditis, acute nephritis and hemorrhage from the mucous surfaces. Recurrence is a special feature of the disease and attacks may come on month after month or even throughout a long period of years. Variability in skin lesions is the rule, and a case may present in one attack the features of an angioneurotic edema, in a second of a multiforme or

Reprinted from the BRITISH JOURNAL OF DERMATOLOGY, *No. 141, Vol. 12.*]

THE

VISCERAL LESIONS

OF

THE ERYTHEMA GROUP.

BY WILLIAM OSLER, M.D., F.R.S.,

Professor of Medicine, Johns Hopkins University.

IN December, 1895,† I published a series of eleven cases characterised by—

I. Polymorphous skin lesions: (*a*) acute circumscribed œdema; (*b*) urticaria; (*c*) purpura; and (*d*) ordinary exudative erythema.

II. Polymorphous visceral lesions: (*a*) local serous or hæmorrhagic exudate in the walls of stomach or bowels, causing (1) crises of pain and (2) hæmorrhages; (*b*) acute nephritis; and (*c*) certain rare pulmonary and other lesions.

III. Infiltration of synovial sheaths, peri-articular tissues, and arthritis.

It would have been better, as some of my dermatological friends suggested, not to have described the cases under the name erythema exudativum multiforme, the term which has been used to designate the so-called pure type of polymorphous erythema, but it was really very difficult to find a name under which to group the cases. Duhring has suggested that the majority of them should be regarded as purpura rather than erythema, but in only Cases 6, 7, and 11 was purpura the sole lesion, while in the remaining cases there was exudate (either serous or hæmorrhagic or both), with swelling.

In the following communication I shall give the subsequent history

* Paper prepared for the Jacobi Festschrift, New York, 1900.

† *American Journal of the Medical Sciences: cf. Brit. Journ. of Dermat.* Vol. VIII., p. 55.

nodosum erythema, and in a third those of peliosis rheumatica. The attacks may not be characterized by skin manifestations; the visceral symptoms may be present, and to the outward view the patient may have no indications whatever of erythema exudativum. Of the eleven cases here reported the visceral manifestations were as follows: In all gastro-intestinal crises, colic, usually with vomiting and diarrhea, five had acute nephritis, which in two cases was followed by general anasarca and death; hematuria was present in three cases; hemorrhage occurred from the bowels in three cases, from the stomach in two cases, from the lungs in two cases, from the nose in three cases; one patient had spongy and bleeding gums; two cases presented enlargement of the spleen; in one case there were recurring attacks of cough and bronchitis without fever; in one case there was a heart murmur. Five of the cases had swelling about and pain in the joints.... The remarkable tendency to recur is a feature of all forms of exudative erythema. It will be noted that of the cases here reported in only one was the attack single. In the others there were multiple outbreaks distributed over periods ranging from two months to eight years.... A remarkable circumstance, which I had not seen mentioned in the literature, is the recurrence of severe attacks without cutaneous manifestations. In the first two cases, which are at present under observation, one would not for a moment suspect the true nature of the disease from the existing manifestations, which are entirely visceral."

In his third article published in 1903, he analyzed his total series of twenty-nine cases. In addition to the visceral manifestations which he had previously described he added two cases with central nervous system symptoms; in one, active delirium at the time of recurring attacks, while in the other there were five or six attacks of aphasia and hemiplegia with cerebral and cutaneous manifestations lasting over a period of fourteen years. He states that it is not improbable that these transient attacks were due to vascular changes in the brain, the counterpart of these occurring in the skin. In describing the respiratory manifestations he cites one case in which there was protracted pneumonia following directly upon a severe attack of exudative erythema. He states that it is likely that the recurring skin lesions, the pneumonia, the general glandular enlargement, and the fatal nephritis were due to one and the same cause. In reference to the cardiac manifestations, Osler stated that he had seen only one case of acute endocarditis, but that there were a good many such instances described in the literature. Three of the cases in his series had heart murmurs and one had pericarditis occurring as a terminal event. In fourteen of his cases there was an acute nephritis, indicated by albumin and numerous tubular casts and in seven cases hematuria. The

seriousness of the nephritis was emphasized by the fact that five of the seven patients died with uremia. Arthritis or arthritic pains were present in seventeen cases. The joint lesions were slight, as a rule, and in no case was there a severe polyarthritis. In many cases there were hemorrhages from the mucous membranes, including epistaxis, blood in the stools and in the urine. In one case the final symptoms were those of severe purpura hemorrhagica after outbreaks of urticaria for many years.

Some of the details of these manifestations so clearly described by Osler have been filled in since the publication of his article, and much progress has been made in recognizing the morphological lesions characteristic of this disease. However, until some certain diagnostic method is at hand the broader aspects of its clinical manifestations will remain incomplete. Many who have subsequently reported similar cases have not pointed out the significance of Osler's contribution. In 1924, Libman and Sacks (4) described four cases under the title "A Hitherto Undescribed Form of Valvular and Mural Endocarditis". All showed the same distinctive clinical picture, two with and two without skin manifestations, and all had a form of endocarditis which they designated as atypical verrucous endocarditis. Dr. Libman stated that this demonstrated that the clinical picture first described by Kaposi (5) and amplified by later observers may occur in the absence of any eruption. This fact had been clearly pointed out some thirty years ago by Dr. Osler. The subsequent contribution of Gross (6), in describing the peculiar histological changes of so-called atypical verrucous endocarditis in the endocardium and pericardium of the majority of cases of lupus erythematosus unaccompanied by a macroscopic endocarditis, did much to clarify the whole subject. A large series of cases was presented by Baehr, Klemperer and Schifrin (7) in 1935 under the title "A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus)." They described the widespread vascular lesions and believed that the disease had a vascular origin. In 1936, Friedberg, Gross and Wallach (8) described cases under the title "Non-Bacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions". These appear to be instances of lupus erythematosus disseminatus without skin lesions, a condition which was clearly recognized by Osler.

Klemperer, Pollack and Baehr (9) described the pathology of disseminated lupus erythematosus in 1941. They stated that the characteristic organic changes, previously considered as heterogeneous, could be understood as local manifestations of the widespread damage of collagen tissue, and that lupus erythematosus could no longer be regarded as a disease with predominant localization in a single organ or as a diffuse disease of the peripheral circulation. In a subsequent paper (10) they pointed out the fallacy of considering diseases in which alterations in collagen tissues predominate, such as rheumatic fever, disseminated lupus erythematosus, scleroderma and allergic states, as being necessarily related etiologically. They suggest that a derangement of the colloidal state of the entire collagenous tissue system may exist. Such a derangement may have a variety of causes.

THE CLINICAL MANIFESTATIONS OF DISSEMINATED LUPUS ERYTHEMATOSUS

It is appropriate to review the current status of the knowledge of the clinical picture of this disease syndrome. This analysis is based on a series of thirty-two cases seen in this hospital in recent years, in all of whom the diagnosis was proved by pathological examination.

It has frequently been emphasized that this disease occurs predominantly in females in the age group from ten to thirty. In the largest previously reported series, that of Baehr, Klemperer, and Schifrin (7), there were twenty-two females and only one male. Nine of the patients were between ten and twenty years of age and nine were between twenty-one and thirty. In the present series there were ten males and twenty-two females. Twenty-five of the patients were white and seven colored. The age distribution was as follows: one to ten—1, eleven to twenty—7, twenty-one to thirty—3, thirty-one to forty—12, forty-one to fifty—5, fifty-one to sixty—2, sixty-one to seventy—2.

Of these thirty-two patients six were still living at the time of the last observation and twenty-six had died. The average duration of the disease from the onset of the first symptoms to death was four years and four months.

In view of the difficulty in making this diagnosis when the characteristic skin manifestations are not present, it is of some interest to see what the initial manifestations were in this series of patients.

Most prominent were joint manifestations which formed the initial complaint in seventeen patients. In fifteen of these there were objective findings and the other two complained of arthralgia. A characteristic skin eruption was the first finding in thirteen of the patients. In six there was unexplained fever and a complaint of weakness. Weight loss, gastro-intestinal disturbances and hemorrhagic phenomena were present in three.

If one now considers the incidence and type of the various manifestations during the entire course of the disease, the complexity of the clinical picture becomes more evident. Fever was a constant manifestation in the active stage. Several of the patients had high unexplained fever as the sole clinical manifestation, and only at autopsy was the definite cause of the fever explained. Elevation in temperature of a significant degree which could not be accounted for other than as a manifestation of this disease was recorded at some stage in thirty of the cases. Chilly sensations were frequently noted by the patient during the febrile periods.

Twenty-seven of the thirty-two patients complained of pain in many joints during the course of the illness. The joint pains were often migratory, and occurred in episodes not infrequently separated by many months or even years. In many instances the changes led to deformity, sometimes anklyosis, and quite frequently muscle atrophy and contractures. A diagnosis of typical rheumatoid arthritis was often made. Generally there were objective changes in the joints including local heat, redness, and swelling; but, occasionally, although the patients complained bitterly of arthralgia, little was found on examination.

The arthritic changes may occur early before skin or other visceral manifestations appear. This is well illustrated by the following case summaries:

Case 1 (JHH 441345), a forty-six year old white woman, who six years before death developed pain localized to the knees, ankles, shoulders, elbows, wrists and fingers. Pain was accompanied by swelling of the involved joints with redness. These manifestations fluctuated in intensity. Three years before death she received two injections of gold which were followed by no untoward manifestations. Six months before death, at a time when she was free of any acute joint manifestations, but did have flexion contractures of both elbows and limitation of motion of the fingers, she developed anorexia and generalized fatigue. Following this

there was rapid loss of weight and the onset of an irregular fever with occasional chilly sensations. Three months before death she was admitted to a hospital for study where she was found to have a severe anemia and leukopenia for which no cause could be found. At this time she complained of intermittent episodes of severe epigastric discomfort, but radiological examination revealed no organic gastro-intestinal lesions. One month before death, on admission to this hospital, she had a temperature of 100.4, pulse rate of 110. She was very emaciated and quite weak. There was definite general glandular enlargement. Typical findings of rheumatoid arthritis with ulnar deviation of the fingers were described, and there was a sclerodermatous appearance to the skin with atrophy of the muscles surrounding the joints. There was also some generalized muscular atrophy. Shallow ulcers were seen on the soft palate. The heart was slightly enlarged to the left. The aortic second sound was accentuated, and there was a systolic murmur at the base. To the left of the sternum there was a pericardial friction rub. A protodiastolic gallop rhythm was heard at the apex. The liver edge extended two fingerbreadths below the costal margin. During the next month she had a fluctuating fever with temperature rising to 101 or 102°F. each day. Four days before death she had a Jacksonian type of convulsion with deviation of the eyes to the left, winking of the lid, facial twitching and clonic movements of the left arm and leg. There were numerous such episodes from that time until her death. She became comatose, and there was paresis of the left side of the body. Laboratory examinations revealed red blood count 2.3 million, hemoglobin 8 grams, white blood count 3.7 thousand with 18% myelocytes, 6% juveniles, 19% polymorphonuclear cells, 53% lymphocytes, 4% monocytes. Stool examination showed a positive quaiac test for blood. Examination of the urine was normal. At autopsy the classical lesions of lupus erythematosus were found. Histological examination revealed hyaline necrosis of collagen with overlying fibrinous thrombus at the base of the mitral valve; foci of collagen degeneration with associated inflammatory cells in the myocardium and about the esophagus; periarterial fibrosis in the spleen and hyaline masses in many glomeruli; organized and fresh pleuritis and pericarditis; anaphylactoid type of pneumonitis; fibrinoid degeneration of the walls of the arteries in the stomach and bladder with aneurysm formation (Fig. 1); intracerebral and subdural hemorrhage in the region of the left occipital lobe (Fig. 2). *During the course of this patient's illness there were never any cutaneous lesions.*

Case 2 (JHH 248475), a thirty-five year old colored male entered the hospital three years before death because of a polyarthritis accompanied by vomiting, chills and fever. Everyone who saw the patient made the diagnosis of rheumatoid arthritis. The white cell count was 3,440 and the hemoglobin was 11.5 grams. Differential count showed 5% myelocytes, 21% juveniles, 38% adult polymorphonuclears, 1% basophiles, 23% lymphocytes, 12% monocytes. The patient was followed in the Arthritis Clinic for many months where treatment with gold was given. It was noted at the start of treatment that the total serum protein level was 8.78 grams, with a globulin level of 5.59 grams. He received a total of 12

FIG. 1. FIBRINOID DEGENERATION IN WALL OF A GASTRIC ARTERY WITH ANEURYSM FORMATION (CASE 1). AUTOPSY 20921

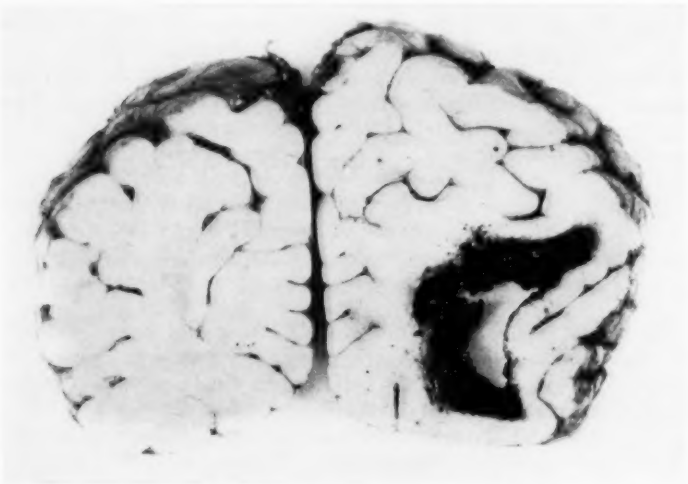


FIG. 2. Intracerebral hemorrhage (Case 1). Probably secondary to lesions of the cerebral arteries similar to that seen in Figure 1. Autopsy 20921.

weekly injections of gold at the end of which time his joint manifestations had subsided, and the patient did not return for observation. Five months before death he began to lose weight and noted the onset of anorexia, night sweats, pains in the ankles and wrists and bleeding from the gums. One month before death he developed pain in the left lower quadrant, had a chill and began to vomit. A short while later he developed a pleuritic type pain in the left chest. On examination three weeks before death the temperature was 99.6, pulse 120, respirations 30, blood pressure 210/155. The patient was very emaciated and looked chronically ill. There were numerous round light colored maculae over the legs. There was fusiform swelling of the phalangeal joints, limitation of motion and some deformity of both wrists. The eyelids were quite swollen, and the tissues over the eye ball were very red and edematous. Examination of the retina showed many exudates and numerous hemorrhages. The heart was slightly enlarged to the left. There was a soft apical systolic murmur. The liver and spleen were not palpable. Laboratory examinations revealed hemoglobin 13 grams, white blood count 5,900. The urine showed a specific gravity of 1020 with 4+ albumin, occasional red blood cells and white blood cells and 2 to 3 hyalin and granular casts per high power field. X-rays of the hands and feet showed the changes seen in chronic rheumatoid arthritis. Blood non-protein nitrogen was 50. Total serum protein was 8.38 with 5.07 grams of globulin. A week before death there was a very rapid increase in the size of the heart and the pulsations were noted to be rather feeble. Fluoroscopic examination revealed a cardiac outline compatible with the presence of a pericardial effusion. The patient ran an irregular fever during the three weeks before death. Ophthalmoscopic examination revealed thrombosis of the right central retinal vein. The patient continued to have attacks of abdominal pain. Autopsy examination revealed the typical lesions of lupus erythematosus. There were onion-skin lesions about the splenic arterioles. Fibrinous pericarditis was found as well as a fibrinous pleurisy. There were hemorrhages in the pleura, endocardium and quadriceps muscle.

Cutaneous lesions appeared during some phase of the illness in twenty-six patients. Weakness, weight loss and easy fatigability were frequently associated symptoms. In addition to the characteristic erythematous eruptions encountered it should be noted that in six individuals purpuric manifestations were the central feature. In two patients cutaneous pigmentation only was noted, and urticaria was the predominant type of lesion in another. It should be stressed that the lesions were not confined to the skin. In ten of the thirty-two patients ulcerative lesions of the oral mucous membranes were observed.

A significant degree of generalized lymphadenopathy was described in sixteen of the patients. In addition, there was localized glandular

enlargement in another six, usually involving the axillary and cervical glands. In the remaining ten patients no significant alteration in the size of the lymph nodes was described. Occasionally the lymphadenopathy was prominant enough to suggest the possibility of some type of lymphoma.

The analysis of the renal manifestations in this group of cases who died and came to autopsy brings out certain points of interest. In two patients there were no renal manifestations during life and no lesions of lupus erythematosus were found in the kidneys. In one instance clinical examination was entirely normal, but the classical lesions were found in the kidneys at autopsy. Twelve of the patients had an abnormal urinary sediment with abnormal renal function and the only kidney abnormalities found at autopsy were due to lupus erythematosus. In seven instances an abnormal urinary sediment was described during life but renal function tests were entirely normal, and in all instances the renal manifestations of lupus erythematosus were the only histological abnormalities found. Eight patients developed a significant degree of azotemia for which no basis could be found other than the lesions of lupus erythematosus in the kidneys. The other patient had multiple renal abscesses. Only four patients in the entire group had a significant degree of hypertension. In two of these the only renal lesions found at autopsy were those of lupus erythematosus. In one patient the kidneys were entirely normal on histological examination, and in the other the only abnormalities were those produced by arterio- and arteriolosclerosis with no changes characteristic of disseminated lupus being found.

The occurrence of pulmonary manifestations during the course of lupus erythematosus has been repeatedly emphasized. In nineteen of the thirty-two cases in the present series there were clinical evidences of pulmonary involvement at some time during their course. Clinical evidence of pneumonia was a very common finding, particularly in the terminal stages, and was often thought to be part of the picture of lupus erythematosus. However, in only three cases were the classical lesions of this disease found at autopsy. In most instances the pneumonia was lobular in distribution and of bacterial origin. In one case there was a bilateral empyema and in another a pyogenic lung abscess.

Two cases showed active pulmonary tuberculosis with cavitation. In one of the patients with pulmonary lesions due to lupus erythematosus physical examination of the chest showed nothing remarkable. X-ray study revealed a non-tuberculous type of infiltration throughout both lung fields (Fig. 4). At autopsy Dr. Rich reported the presence of typical lesions of lupus erythematosus in the lungs, and no other pathological abnormalities were present. In another case, examination revealed transient medium and coarse rales in various areas of both lung fields posteriorly. X-ray examination showed an increase in hilar markings spreading out into both lung fields suggesting either infection or congestive change. At autopsy the findings of "anaphylactoid or rheumatic pneumonia" were described, and there was no evidence of any bacterial invasion. In the other instance there was no suggestion on physical examination or by x-ray of any abnormality in the lungs. At autopsy very small, scattered areas were seen in which the typical lesions of lupus erythematosus disseminatus were described.

Osler pointed out that the course of the pneumonic manifestations might be very protracted. Rakov and Taylor (11) reported a case without cutaneous manifestations in which persistent signs of consolidation of the lungs were the most prominent feature of the clinical course, persisting from early after onset of symptoms until death eight months later.

Involvement of the various serous membranes has been described as a common clinical feature of this disease. Nine of these patients had a fibrinous pericarditis, while in three there was, in addition, a small effusion. The shape of the cardiac silhouette was characteristic, but the degree of effusion was never sufficient to produce any clinical evidence of cardiac tamponade. In eleven patients pleuritis was discovered at autopsy; free fluid was present in almost half of these cases, in certain instances being large in amount and bilateral. In no instance was there ascites in the absence of generalized edema. Two patients had clinical evidence of peritoneal irritation. This led to the impression in one that the patient had an acute abdominal condition requiring surgery, but operation revealed only tissue edema. Evidence of involvement of the peritoneal surfaces revealed at autopsy was

unusual except for mild perisplenitis and perihepatitis. Three patients complained of severe myalgia and in two instances this, together with muscular atrophy, led to the clinical diagnosis of dermatomyositis.

Seven of the patients at postmortem examination were found to have verrucous vegetations on one or more of the heart valves similar to those described by Libman and Sacks (4). In only one instance did these alterations of the valves seem to be associated with any impairment of cardiac function. In this individual verrucous vegetations

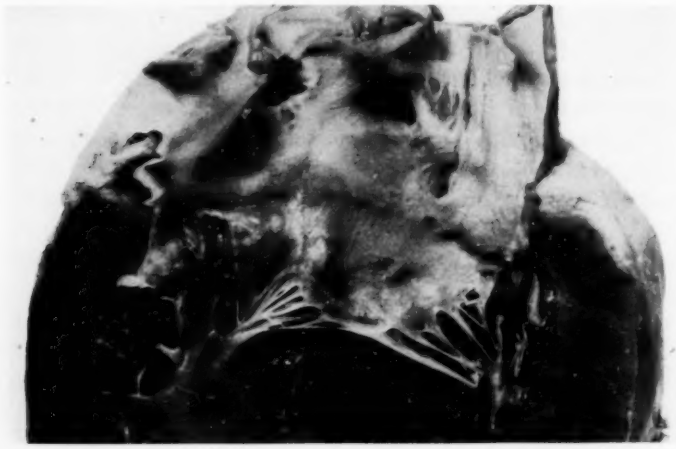


FIG. 3. SMALL ORGANIZING VEGETATIONS ON MITRAL VALVE
(J. A., AUTOPSY 17346)

were found on the mitral valve which was thought to be so altered by these changes as to result in insufficiency. The left heart was dilated and enlarged and the patient showed evidences of heart failure both prior to death and at postmortem examination. The patient was seen by Dr. Louis Hamman who described enlargement of the left ventricle, the presence of a gallop rhythm, and a loud first sound in the mitral area. This was followed by a blowing systolic murmur and a sound in diastole which was thought to represent a diastolic murmur. The blood pressure was 160/95. In the other instances in which verrucous endocarditis was found at autopsy the only associated physical altera-

tion noted during life was a soft apical systolic murmur. Murmurs of this type were not infrequently noted in patients who died and whose

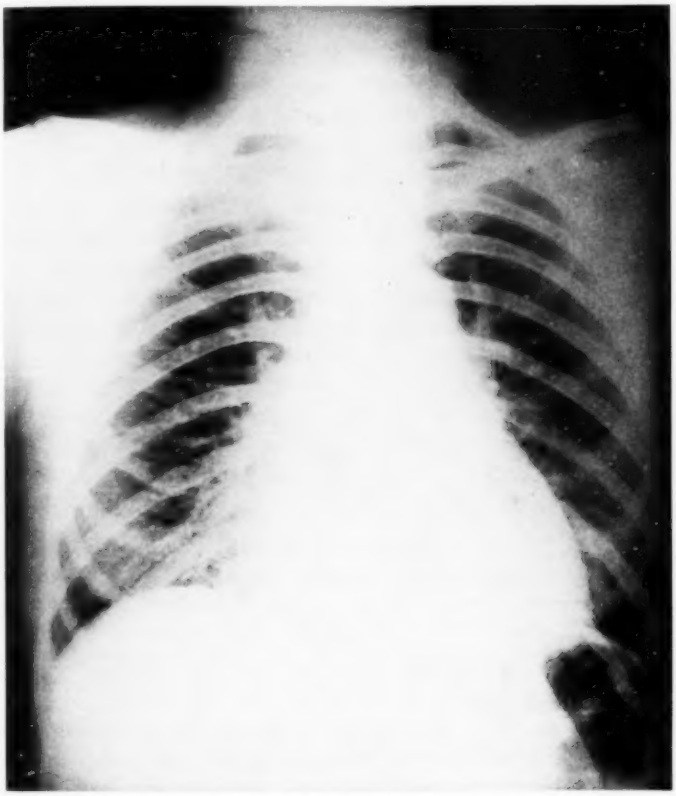


FIG. 4. X-ray of chest (Case 6), showing extensive non-tuberculous pulmonary infiltration and enlargement of the cardiac silhouette due to pericardial effusion. Histological examination revealed focal hemorrhages and focal alveolar exudate in lungs, with organization, thought to be typical of the changes seen in rheumatic fever, periarteritis nodosa, and sulfonamide hypersensitivity. (Autopsy 19429.)

valves were found to be perfectly normal at autopsy. Of much greater significance, in so far as the development of cardiac insuffi-

ciency was concerned, was the presence of myocardial scarring secondary to arteritis and ischemic necrosis of the myocardium. Of interest is one patient who at autopsy was found to have verrucous vegetations of the mitral, aortic, and tricuspid valves (Fig. 3). Streptococci were found imbedded in the verrucous vegetations involving the tricuspid valve. It was thought that this patient had a secondary bacterial endocarditis establishing itself in a valve previously involved by the endocarditis of disseminated lupus erythematosus.

In the series of cases reported by Osler, gastro-intestinal manifestations were emphasized. Since that time, in the cases described in the literature such manifestations have been insignificant in most instances. This has led some authors to the conclusion that most of the patients described by Osler did not have lupus erythematosus disseminatus. In the present series five patients had a significant degree of diarrhea. In four of these the stools were bloody, and one had a massive hemorrhage. In four cramping abdominal pain was a prominent symptom. In other patients extensive lesions of classical lupus erythematosus have been found in the vessels of the gastro-intestinal tract. The following case illustrates the occasional prominence of abdominal manifestations in the clinical picture.

Case 3 (JHH 227999), a forty-five year old white male who developed unexplained fever and diarrhea in October, 1940. After a few days there was spontaneous remission, but he continued to have bouts of fever and diarrhea throughout the winter. Stool examinations and x-ray studies were done, but no basis for his complaints could be demonstrated. In March, 1941 fever and diarrhea returned with severe epigastric discomfort. The following month his temperature rose to 103° to 105°F. each day for short periods of time interspersed with periods of normal temperature. During the course of the fever he complained of chilly sensations and developed "lumps in the muscles." In May, 1941 he developed an erythematous eruption which was most prominent over the "butterfly area" of the face, and he was found to have both a pleural and pericardial effusion. Renal impairment was evidenced by albumin, white cells, and red cells in the urine and a non-protein nitrogen level of 59 mgm. %. His condition grew rapidly more critical, and he died on May 17, 1941. At autopsy the classical lesions of lupus erythematosus disseminatus were found with endocarditis, hyaline masses in the glomerular loops, and perivascular fibrosis of the splenic arteries. There was a bilateral hydrothorax and a fibrinous pericarditis. Figure 1 shows the type of vascular lesions which are found in the gastro-intestinal tract. The clinical manifestations of this patient are described above (Case 1).

Enlargement of the liver to a significant degree was noted frequently both clinically and at postmortem examination. This enlargement was due in most instances to the deposition of large amounts of fat. Occasionally widespread necrosis of liver tissue was observed. It is interesting that in only one instance was jaundice noted in this group of patients, and this was of the obstructive type. This patient had generalized edema with ascites, and the jaundice was due to edema of the biliary ducts. In only a small number of patients was liver function adequately studied. In these cases there was evidence of diffuse parenchymatous disease manifested by elevation of the cephalin flocculation and the thymol turbidity. These tests were abnormal even in instances in which the albumin-globulin ratio was not altered. In no instance, however, were the lesions of lupus erythematosus disseminatus seen in histological examination of the liver. Focal central necrosis and excess fat were present in six of the cases described by Coburn and Moore (12). The nature of these changes deserves further study.

A palpable spleen was noted in less than half of the cases, and the enlargement was only moderate in those instances. Kaposi (5) reported an instance of acute lupus erythematosus in a female aged 15, the skin manifestations making their appearance about eight days after the onset of purpura hemorrhagica. Osler also recognized the occurrence of purpura hemorrhagica in the series of cases which he described. Too much significance, however, cannot be attached to these observations as at that time the hematological criteria for the diagnosis of thrombocytopenic purpura were not established. In 1933, Lyon (13) described a twelve year old boy who had thrombocytopenic purpura with leukopenia. Subsequently, the patient developed the typical skin lesions of acute lupus erythematosus. In 1937, Keil (14) described the case of an eighteen year old white female who developed thrombocytopenic purpura. The patient had a satisfactory response to splenectomy. However, eighteen months later she returned to the hospital with the characteristic skin manifestations of lupus erythematosus. The patient died almost seven years after her first appearance, apparently in uremia. Jones and Tocantins (15) reported the case of a female patient who developed lupus erythema-

tosus several months after splenectomy for thrombocytopenic purpura, at a time when the platelet count was restored to normal.

In the present series of cases thrombocytopenic purpura occurred in four and in all of them the characteristic lesion of periarterial fibrosis was found in the spleen on histological examination.

The following case bears certain similarities to those previously reported in the literature:

Case 4 (JHH 274052), a thirty-nine year old white female who for a period of eleven years had had a recurrent eruption over the face each summer following exposure to the sun. Three years before death she had developed severe metrorrhagia and gave a history of easy bruising. At the time of examination there were numerous purpuric spots and ecchymoses on the skin. Examination of the blood showed a hemoglobin of 9.8 grams, white cell count of 3050 and a platelet count of 41,000. The differential white cell count was normal. The patient was seen by Dr. Wintrobe who made a diagnosis of thrombocytopenic purpura. During observation over a period of several months there was no improvement; the platelets remaining between 30,000 and 50,000 with the bleeding time ranging from 8 to 14 minutes. Bone marrow examination showed no platelet-producing megakaryocytes present. A splenectomy was done and review of the sections by Dr. Arnold Rich revealed the typical lesions of lupus erythematosus. Following operation her white cell count rose to 19,800 and the platelet count to 150,000. The bleeding time returned to normal, and the menstrual flow became normal in amount. During the next three years, with the exception of the facial eruption during the summer months, the patient felt quite well. Thirty-six hours after the final admission she developed anorexia and fever accompanied by pain in the muscles, joints, and skin. At the time of admission to the hospital she was acutely ill with a high fever. The skin was warm and moist, and there were numerous purpuric spots over the malar eminences. There was an erythematous blush over the chest and abdomen. The following day the purpuric eruption over the bridge of the nose was found to be even more marked, and the erythema over the chest had developed a dark purplish color. Blood culture and spinal fluid culture revealed type 12 pneumococcus. The patient was in severe peripheral circulatory collapse and died within forty-eight hours of her admission to the hospital. Examination of the blood showed a hemaglobin of 14.5 grams with 12,600 white cells. The platelet count was 42,000.

A second patient has had no further bleeding tendency for eight years following splenectomy for thrombocytopenic purpura and has developed no manifestations of disseminated lupus erythematosus, although histological examination of the spleen showed the characteristic type of periarterial fibrosis.

Case 5 (JHH 207012), a twenty-four year old white female who entered the hospital in July, 1940 complaining of the appearance of purpuric spots on the legs, thighs and buttocks over a period of five weeks. Examination at that time showed numerous petechiae over the entire body, small ulcerations on the lower lip, bleeding gums and hemorrhage from the nose. Hemoglobin was 11.2 grams, white cell count 6,250 with normal differential. The bleeding time was greater than fourteen minutes. Tourniquet test was strongly positive. Platelet count was 50,000. After operation the platelet count did not rise until the fourth day when it reached 300,000. At that time bleeding had ceased, and the bleeding time was one minute. The clot which did not retract after four days prior to operation now began to show retraction in one hour which was complete in twelve hours. The spleen showed hyperplasia of the malpighian bodies as well as numerous lesions of periarterial fibrosis described by Dr. Rich as characteristic of those seen in lupus erythematosus disseminatus.

The most that can be said of this group of cases is that there was thrombocytopenic purpura, and that the characteristic lesions of lupus erythematosus were found in the spleen.

The presence of anemia in this condition has been emphasized. Fourteen patients in this series developed a moderate degree of anemia, and in an additional eleven it was progressive in severity. In the remaining seven no depression of the erythron was noted at any time during the course of the illness. Thrombocytopenia has been regarded by some as a characteristic feature of disseminated lupus. Only five of these thirty-two patients showed an appreciable reduction in the number of circulating platelets. Four of these patients had the clinical picture of thrombocytopenic purpura as mentioned above. Leukopenia has also been described as a very frequently encountered alteration in the blood picture of patients with this disease. Eighteen of the group showed at some time during the course of their illness a total white cell count of less than 5,000 per cu.m. Attention should be called to the fact that when patients with a significant degree of leukopenia acquired a secondary bacterial infection, leucocytosis developed with counts rising as high as 25,000 per cu.m. in some instances.

Nervous system manifestations which were directly attributable to the lesions of lupus erythematosus formed an important feature of the clinical picture in many of these patients. In four, convulsive episodes of a generalized nature were described. In an equal number

there was a toxic psychosis which necessitated care in a psychiatric hospital in two instances. Three patients had transient periods of coma with no basis other than the disease under discussion. In an equal number of patients a hemiplegia (see Case 1) developed. In two others there were transient episodes of bilateral ptosis, and in one repeated attacks of Jacksonian epilepsy (see Case 1). In several instances there were delirium, coma or convulsive episodes probably associated with uremia, no other lesions being found in the kidneys than those of disseminated lupus.

The following case illustrates the type of psychotic behavior which may develop during the course of this disease.

Case 6 (JHH 345215), a forty-five year old white female developed an eruption over the malar surfaces of the face and generalized arthritis in August, 1944. At times there was some heat, redness and swelling of the joints, but these were never conspicuous. She lost strength rapidly, and edema of the ankles appeared. In December, 1944 she developed very erratic behavior, wandering off for several days at a time without informing her family of her whereabouts. This abnormal behavior was periodic up until the time of her admission on March 2, 1945. At that time there was a classical erythematous eruption of lupus erythematosus over the malar eminences. There was definite peri-orbital edema, and the conjunctivae were injected. Small lymph nodes were palpable in the axillary and inguinal regions. There was a gallop rhythm over the entire precordium, and a loud systolic murmur was heard over the base. There was pitting edema up to the region of the mid-thighs. Laboratory examinations revealed hemoglobin 10.5 grams, white cell count of 4,550. The urine contained 4+ albumin and an occasional red cell and white cell as well as granular cast. Electrocardiogram showed some prolongation of the auriculo-ventricular conduction time. She was extremely restless. Feeding was difficult because of her inaccessibility. She soon became entirely unresponsive; tossing and turning in bed so that restraining sheets were necessary. Occasionally, she would make a cry, wordless and animal-like. Choreiform movements were described. Tube feeding was attempted, but was very difficult because hemorrhages occurred when the tube was inserted. The patient never regained consciousness. Terminally, the non-protein nitrogen rose to 70 mgm. %, but during the major period of the delirium it was never higher than 32 mgm. %. At autopsy the patient was found to have lupus erythematosus with verrucous endocarditis, periarterial fibrosis in the spleen and classical lesions in the kidneys. There were focal hemorrhages and focal areas of alveolar exudation in the lungs with organization. Periarteritis nodosa-like lesions were described in the ovaries and tubes. Bilateral pleural effusions and ascites were noted. Numerous old and fresh petechial hemorrhages were found throughout the brain substance.

In 1940 Maumenee (16) described the retinal lesions in four patients with acute disseminate lupus erythematosus and of one patient with the chronic type. He noted the following typical lesions: (1) small fluffy white spots located in the superficial layers of the retina never

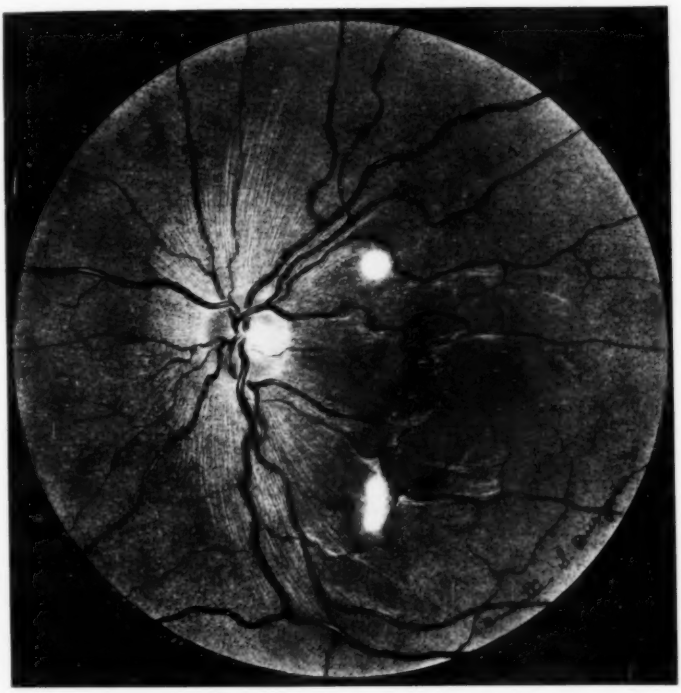


FIG. 5. TYPICAL CYTOID BODIES IN THE RETINA; CONFIRMED BY HISTOLOGICAL EXAMINATION (M. O., JHH 57321)

larger than the disc and usually in the posterior part of the fundus. These were very similar in appearance to the exudates seen in hypertensive retinopathy. Histologically they were all shown to be areas of cytoid bodies; (2) small hemorrhages placed superficially in the retina and not located in relation to the white patches nor to the larger retinal vessels. Microscopically these hemorrhages were found to lie

in the nerve fiber layer of the retina. (3) Slight papilledema. In seven of the cases in the present series the typical cytoid bodies (Fig. 5) and superficial retinal hemorrhages have been seen. In one instance the significance of these lesions was recognized by the Ophthalmological Consultant in a patient who had unexplained fever, splenomegaly and repeated epistaxes. At a later date the classical features including the typical cutaneous eruption appeared. One patient in this series developed thrombosis of the central retinal vein. Thus, among patients with disseminated lupus erythematosus, lesions in the retina occur fairly frequently. These lesions are not specific, but in instances in which there is no hypertensive vascular disease they may furnish a very important clue, particularly when the other visceral manifestations are not accompanied by the cutaneous lesions. It seems possible that from more detailed study of the retina in a larger number of cases, with more accurate description of the nature and course of the lesions, a reasonably characteristic and diagnostic ophthalmoscopic picture might evolve.

It has been pointed out that the skin lesions in this disease frequently appear after exposure to sun light. This photo-sensitivity has been evident in many of the cases in this series. In one patient typical "butterfly lesions" appeared over the face each successive summer following exposure to the sun over a period of twelve years. (Case 4.) Rich (17) has recently pointed out that disseminated lupus erythematosus, in common with rheumatic fever and periarteritis nodosa, presents a rather impressive variety of lesions each of which occurs in anaphylactoid reactions of the serum sickness type; such as fever, urticaria and erythematous skin eruptions, purpura, arthritis, necrotizing inflammatory arterial lesions, focal collagen degeneration, focal necroses of lymph nodes and of spleen, myocarditis, valvulitis, sterile inflammation of serous membranes, sterile pneumonitis and transient paresis. Clinically it has not been possible to demonstrate hypersensitivity to any given substance in cases of lupus erythematosus disseminatus which might be considered as a causative factor. However, the following case is of interest in this regard:

Case 7 (JHH A-30617). This twelve year old white boy developed pains in the wrists and shoulders in 1942 at which time he was discovered to have a markedly elevated sedimentation rate. When first examined in June, 1943 he had

fever and still complained of joint pains. Physical Examination at that time showed temperature 102°F., pulse 115, respirations 20, blood pressure 120/75. There were no other abnormalities. The sedimentation rate was 29 mm./hr. corrected. During the next few weeks he ran a persistent elevation in temperature, complained of joint pains and developed general glandular enlargement. In December, 1943 a shower of purpuric spots occurred over his lower extremities and the palms of his hands. After that time crops of petechiae appeared at intervals, and he had frequent nosebleeds. Early in January he developed gross hematuria and slightly bluish non-tender nodules on the palms of the hands, on the elbows, and on the feet. These would develop and disappear within the course

FIG. 6. Note the characteristic distribution of the facial lesions and the evidence of oral hemorrhage (Case 7).

of thirty-six hours. One of these nodules was biopsied and showed the classical lesions of lupus erythematosus. The patient was found to have a marked reaction to a beta streptococcus antigen. Two doses of 0.1 cc. of a special streptococcus vaccine were given intracutaneously at a time when the previously described manifestations were quiescent. Following the second dose his temperature rose to 40°C. and numerous nodules appeared beneath the skin, first being noted six hours after the injection; he developed generalized pruritis and a diffuse erythematous eruption. Scattered showers of petechiae appeared with increasing frequency. The temperature remained markedly elevated and a few days later he vomited 400 cc. of blood. Four days after the first injection he developed a typical "butterfly rash" over the malar eminences which was purplish red, slightly raised and sharply outlined (Fig. 6). On March 5 he became comatose, a positive Babin-

ski was demonstrated on the right side with flaccid paralysis of the right arm and stiffness of the left. Numerous flame-shaped hemorrhages were found in the retina of both eyes. At autopsy there were typical wire-loop lesions in the glomeruli and sections of the spleen showed scattered periarterial fibrosis of the onion-skin type. No other lesions characteristic of lupus erythematosus were described.

Coburn and Moore (12) pointed out that hyperglobulinemia is a constant characteristic of the lupus state. Electrophoretic analysis showed that the increase in globulin was chiefly in the gamma globulin fraction. Autopsy study of their patients yielded no evidence that chronic infection was responsible for the production of this protein unless one considered the presence of mild infections of the bronchial tree as of significance. They state that it has been pointed out that the arterial and renal lesions of the lupus state may be referable to the deposition of coagulable material resembling serum protein, and add that "it seems likely that such physical changes may give rise to the vascular phenomena observed during life." They further state, "that disseminated lupus appears to be a disease of disturbed cellular metabolism, perhaps associated with the presence of this reactive protein."

Determinations of serum protein content were made in 22 cases of the present series. The amount of globulin present was greater than three grams per cent in 19, the average value being 4.3. The maximum values were 8.5 for total protein and 5.3 for globulin, while the respective minimum values were 3.94 and 2.06. Those of Coburn and Moore were: maximum 8.7 and 5.7; minimum 4.2 and 2.1. Their mean globulin value was 3.9. In general, there seemed to be, in the present series of cases, a tendency for the patients showing the most marked arthritic manifestations to have the highest values for serum globulin. In those cases without joint manifestations the mean value for serum globulin was only 3.27. This is of interest in view of the fact that in patients with rheumatoid arthritis there is frequently an elevation of the globulin fraction with reversal of the A/G ratio.

It is relatively easy to make the diagnosis of disseminated lupus erythematosus when the patient shows all of the characteristic manifestations including fever, arthritis, cutaneous lesions, sterile effusion in serous cavities, and a picture of chronic nephritis. However, it must be emphasized that the course of the disease is characterized

by fluctuations in the degree of activity which may be great at times followed by periods of relative freedom from symptoms. In the recrudescences the active lesions may be confined to certain restricted areas. For instance, in one attack the only manifestations may be fever and a pleural effusion, while in another the important clinical abnormality may be pericarditis with effusion. In still another the cutaneous manifestations may be quite prominent. In this way the full picture of the disease only unfolds over a period of years, and the patient may be seen in several exacerbations before enough perspec-

TABLE I

The Incidence of Complicating Diseases in 32 Cases Of Lupus Erythematosus Disseminatus

Pulmonary tuberculosis	2
Miliary tuberculosis	2
Tuberculous adenitis	3
Tuberculosis of spine with psoas abscess	1
Pulmonary infarction	1
Lobular pneumonia	8
Type 2 pneumococcal lobar pneumonia	1
Type 23 pneumococcal lobar pneumonia with bacteremia	1
Type 6 pneumococcal lobar pneumonia with bilateral empyema	1
Type 12 pneumococcal meningitis	1
Aspiration pneumonia	2
Staphylococcic pneumonia	1
Beta hemolytic streptococcus septicemia	2
Dural Meningioma	1
Bacterial Endocarditis	1
Multiple renal abscesses with bacteremia	2
Purulent lung abscess	1
Tubo-ovarian abscess, ruptured, with generalized peritonitis	1

tive can be gained to make the diagnosis obvious. Once the diagnosis becomes clear the tendency may be to attribute any subsequent illness to the bizarre and variable clinical manifestations of disseminated lupus erythematosus. The involvement of any given organ or location may simulate a variety of other diseases affecting the same region. It is important to emphasize that any new clinical development occurring during the course of this disease must be analyzed with a completely open mind. An illness entirely unrelated may develop, be unsuspected, and lead to death. This situation becomes all the more important when one realizes that disseminated lupus erythematosus

may have long periods of remission; some patients living for ten to fifteen years or more, with intervals of complete or relatively complete freedom from active symptoms. The accompanying table (Table I) illustrates the variety of complicating diseases which may be seen during the course of lupus erythematosus. The following case report illustrates the difficulty of recognizing these concomitant diseases, and the equal difficulty of evaluating their relative importance in the overall clinical picture.

Case 8 (JHH 260256), a 52 year old white female entered the hospital May 25, 1942 complaining of fever and arthritis of eleven weeks duration. Eighteen months previously she had developed pain and swelling in the hands and forearm which lasted for three months. There was a recurrence of the joint manifestations in March, 1942. The following month examination showed a temperature of 101.4°F., skin and mucous membranes showed mild pallor, and there was symmetrical edema of the hands and feet. The remainder of the examination was not remarkable, except for the leucocyte count of 3,600. She continued to run an irregular fever and developed crisp, inspiratory rales at both lung bases and some pleural pain at the left base. During the next few weeks she became increasingly weak and developed generalized aches and pains necessitating her admission to the hospital on May 25 for further study. Physical examination showed a mild erythematous eruption over the bridge of the nose and the cheeks. The only additional finding was a sustained ankle clonus. The patient continued to run a daily elevation in temperature from 101° to 102°. There was a heavy growth of E. coli in the urine. This infection was resistant to all forms of treatment available, including sulfonamides and mandelic acid therapy. Intravenous pyelograms showed both kidneys to be normal in size, shape and position. On June 29 physical findings indicated a left pleural effusion. Five hundred c.ml. of relatively acellular fluid was removed. On June 3, there was an exacerbation of the cutaneous eruption following a mild exposure to the sun. On August 12, she developed auricular flutter and x-ray of the chest showed enlargement in the region of the left ventricle. On August 31, the patient had the first of a series of convulsions which were tonic and later clonic, being accompanied by aphasia. These occurred at increasingly frequent intervals during the next few days. The patient became much weaker and died on September 5. The final anatomical diagnosis was lupus erythematosus disseminatus, pericardial effusion, organizing perisplenitis; onion-skin lesions in the spleen; minute area of valvulitis; mitral valve; right pleural adhesions; subacute ulcerative and diphtheric cystitis and urethritis; acute pyelonephritis, right kidney; septicemia, E. coli; acute interstitial myocarditis, aspiration pneumonia; fatty liver; history of convulsions, dural meningioma, left parietal lobe.

In this instance the extent and importance of the urinary tract infection was not appreciated, as it was thought to be confined to the bladder. Furthermore, the fever and other manifestations to which this may have contributed were regarded as part of the picture of rapidly advancing lupus erythematosus. Convulsions are a relatively common feature during the course of lupus erythematosus and the presence of a dural meningioma in this case was entirely unsuspected.

An analagous situation existed in Case 4 described above. The final fulminating illness was thought to be due to an acute exacerbation of the disseminated lupus, principally because of the dramatic extension of the cutaneous lesions. Further study, however, revealed that a pneumococcal bacteremia and meningitis was the cause of her final acute illness leading to death.

SUMMARY

It seems evident from this study that Osler constructed a framework for the clinical picture of this disease, and that others have supplied the details. There seems to be little or nothing of real significance, as far as the clinical manifestations are concerned, which he omitted. The frequency distribution of the various features which he emphasized remains essentially the same, with the possible exception of the gastro-intestinal manifestations. He focused attention upon those features of the disease which, as this review makes obvious, are still of paramount importance:

1. The cutaneous lesions have visceral counterparts which may occur in the absence of any dermal abnormalities.

2. While the disease may manifest itself through alterations in any of the organ systems; the cutaneous, joint, and renal manifestations are most prominent.

3. Osler noted that the endocardium was at times involved, and pointed out the occurrence of hemorrhagic manifestations.

4. He emphasized the fact that the disease may have a protracted course, during which varied clinical abnormalities appear, rendering diagnosis difficult unless one has the opportunity to follow the course of the illness over a long period of time.

5. Osler realized the kinship of the diseases of the rheumatic group,

but pointed out the possibility of different etiologies. This thought finds later expression in the belief of Klemperer, Pollack and Baehr (10) that these are clinical entities of varying etiology involving primarily the same "system" of the body; thus, assuming an outward similarity, though etiologically distinct.

6. Just as certain features of the cases in Osler's series were particularly striking, in the group reported here one is impressed by the involvement of the nervous system, the similarity of the joint lesions to those of rheumatoid arthritis, the incidence of thrombocytopenic purpura, and the frequency with which secondary infections have occurred. The difficulty of recognizing these latter complications, in certain instances, in a disease with such widespread lesions is obvious. Equally obvious is the importance of their recognition in the presence of a disease which may run a relatively benign course for many years.

This review has added nothing new to the fundamental expressions of Osler. Perhaps it may serve as an echo of his clinical genius.

We are indebted to Dr. A. C. Woods for the use of figure 5; to Dr. A. R. Rich for permission to use the autopsy material; and to Dr. F. F. Schwentker for the cases from the Department of Pediatrics.

BIBLIOGRAPHY

1. Osler, William: On the Visceral Complications of Erythema Exudativum Multiforme. Am. J. Med. Sc., **110:** 629–646, 1895.
2. Osler, William: The Visceral Lesions of the Erythema Group. Brit. J. Dermat. Lond., **12:** 227–245, 1900.
3. Osler, William: On the Visceral Manifestations of the Erythema Group of Skin Diseases. Tr. A. Am. Physicians, **18:** 599–624, 1903.
4. Libman, E., and Sacks, B.: A Hitherto Undescribed Form of Valvular and Mural Endocarditis. Arch. Int. Med., **33:** 701–737, 1924.
5. Kaposi, M. K.: Neue Beitrage Zur Kenntniss des Lupus Erythematosus. Arch. f Dermat. u Syph., **4:** 36–78, 1872.
6. Gross, L.: The Heart in Atypical Verrucous Endocarditis (Libman-Sacks). Libman Anniv., **2:** 527–550, 1932.
7. Baehr, G., Klemperer, P., and Schifrin, A.: A Diffuse Disease of the Peripheral Circulation (Usually Associated with Lupus Erythematosus). Tr. A. Am. Physicians, **50:** 139–152, 1935.
8. Friedberg, C. K., Gross, L., and Wallach, K.: Non-Bacterial Thrombotic Endocarditis Associated With Prolonged Fever, Arthritis, Inflammation of

Serous Membranes and Widespread Vascular Lesions. Arch. Int. Med., **58:** 662–684, 1936.

9. KLEMPERER, P., POLLACK, A., ABOU, D., AND BAEHR, G.: Pathology of Disseminated Lupus Erythematosus. Arch. Path., **32:** 569–631, 1941.
10. KLEMPERER, P., POLLACK, A., AND BAEHR, G.: Diffuse Collagen Disease. J. A. M. A., **119:** 331, 1942.
11. RAKOV, H. L., AND TAYLOR, J. S.: Acute Lupus Without Cutaneous Manifestations and with Heretofore Undescribed Pulmonary Lesions. Arch. Int. Med., **70:** 88, 1942.
12. COBURN, A., AND MOORE, D.: Plasma Proteins in Disseminated Lupus Erythematosus. Bull. J. H. H., **73:** 196, 1943.
13. LYON, J. M.: Acute Lupus Erythematosus. Am. J. Dis. Child., **45:** 572, 1933.
14. KEIL, H.: Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura. Brit. J. Derm. and Syph., **49:** 221, 1937.
15. JONES, H. W., AND TOCANTINS, L. M.: Purpura Hemorrhagica. Further Notes in the Treatment. Tr. Ass. Am. Physicians., **51:** 59, 1936.
16. Maumenee, A. E.: Retinal Lesions in Lupus Erythematosus. Am J. Ophth., **23:** 971, 1940.
17. RICH, A. R.: Hypersensitivity in Disease. The Harvey Lectures Series, **42:** 106–147, 1946–1947.

THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES.

AUGUST, 1903.

CHRONIC CYANOSIS, WITH POLYCYTHÆMIA AND ENLARGED SPLEEN: A NEW CLINICAL ENTITY.

By William Osler, M.D.,
Professor of Medicine in Johns Hopkins University.

The group of cases here reported, with those collected from the literature, are worthy of careful study, as we have here in all probability "a definite clinical entity and one which is new to medical science," to use the words of Saundby and Russell in describing their case. The condition is characterized by chronic cyanosis, polycythæmia, and moderate enlargement of the spleen. The chief symptoms have been weakness, prostration, constipation, headache, and vertigo. A further analysis will be reserved until after the consideration of the cases:

Case I. *Cyanosis for years, of unknown origin; albuminuria; rapid pulse; polycythæmia; high vascular tension.*—Dr. K., aged forty-four years, consulted me October 28, 1901, complaining of a rapid pulse and diffuse cyanosis. He has been a very healthy man, active and vigorous, of good habits; has had no serious illnesses. He has been uneasy about himself, as he had detected a trace of albumin in the urine. For several years his wife has noticed that he has had a very congested appearance, and the eyes would often be deeply suffused. I have seen him at intervals for the past five years and have known him to be a very blue-faced man. He has been of a constipated habit. His eyes are somewhat prominent, but his wife says this is natural to him. He has constantly a feeling of fulness in the head, sometimes a sensation of vertigo, and for these symptoms he consulted me.

He was a well-built, well-nourished man; the face much suffused; the ears looked a little blue; the conjunctivæ were injected, and the lips distinctly cyanotic. The tongue also looked cyanotic. The general surface of the skin looked suffused and the anæmia left after pressure of the hand on the skin was very marked and very slowly

OSLER'S CHRONIC CYANOTIC POLYCYTHEMIA WITH SPLENOMEGALY

MAXWELL M. WINTROBE

Department of Medicine, University of Utah College of Medicine, Salt Lake City

Although the concept that patients might be overburdened with blood was held by Galen and his predecessors as well as by those who followed him, as late as 1889 the hematologist, Hayem, stated that he did not believe in the existence of a plethoric state which could be ascribed to an increase of red cells (1). This was the authoritative opinion even though transitory hyperglobulia had been noted by Vogel in 1854 and polycythemia in association with chronic heart disease had been observed by Malassez and by Naunyn in 1872 (2). In 1890 Viault (3) found high blood counts in persons living at high altitudes.

In writing in 1892 "Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante", Vaquez (4) attributed the condition to congenital heart disease even though there were no auscultatory signs. He faced the criticism of Hayem in stating that functional hyperactivity of the hematopoietic organs was suggested by the exaggerated volume of the liver and spleen in his patient and was the cause of the increase in red cells, hemoglobin and leucocytes.

Failure to find evidence of congenital heart disease at autopsy made Vaquez's case more mysterious. The unique character of such cases was recognized by Cabot (1899) (5), by McKeen (1901) (6) and by Saundby and Russell (1902) (7) but it was only the last named who appreciated the fact that they were dealing with a new clinical entity. Previously, in 1889 Cuffer and Sollier (8) had described the disorder very adequately but they did not examine the blood.

By the time Osler's report was given it was becoming clear that there are two classes of polyglobulism: relative, in which the condition is due to a diminution in the quantity of the plasma of the blood, and true, in which there is an actual increase in the number of blood corpuscles. Vaquez and his pupil, Quiserne (9), in 1902 had clearly defined true polycythemia and included the disease first described by Vaquez under this head together with conditions in which there is difficulty in proper aeration of the blood, as in high altitudes, or in heart disease, congenital and otherwise.

Osler gave his report before the Association of American Physicians in May, 1903. This was subsequently published in the American Journal of the Medical Sciences (10), of which the first page is reproduced here. Osler gave accent to the supposition of Saundby and Russell that the condition is a definite clinical entity and clearly described the clinical picture.

Osler presented four cases. The first patient was a physician aged forty-four years, seen by him in 1901, who for years had had cyanosis of unknown origin. The patient had detected albuminuria himself. In addition the pulse was rapid (120); there was polycythemia and "high vascular tension" (175–203 mm.). The edge of the spleen was palpable. There were no signs of emphysema and the heart was of normal size with clear sounds. Osler suspected "chronic degeneration of the kidneys, with slight arteriosclerosis". The laboratory work, performed by Dr. Futcher, revealed a few hyaline and finely granular casts in addition to the albuminuria. The red blood corpuscles numbered 9,952,000, the hemoglobin was 120 per cent (Fleischl). Several counts were made as it was thought that there might have been a mistake. The "relative scarcity of leucocytes" (4,000) was another puzzling feature.

The second patient was a Russian Jew, 35 years of age, first admitted in 1900, who complained of recurring attacks of nausea and vomiting, pain in the left side and severe constipation. Persistent and marked cyanosis of the face, hands and mucous membranes, red cell counts ranging between 6,500,000 and 10,200,000, hemoglobins of 102 to 125 per cent and leucocyte counts of 8,600 to 30,000, as well as a blood specific gravity of 1.068 to 1.083 were the chief features. It was noted that the cyanosis persisted even when there was very little vomiting.

The third patient was seen at the Lakeside Hospital in Cleveland with Dr. Lowman. This was a woman of 44 years, of English descent, who was unusually cyanosed and had an enlarged spleen. A double pterygium and failing vision had brought her to the opthalmological division of the hospital but persistent headache attracted the attention of the internists. In this, as in the preceding cases, it was noted that the impression made on the skin with the finger disappeared slowly. The spleen extended 7.5 cm. below the costal margin. The poly-

cythemia was even more pronounced than in the other two cases: 11,616,000. The leucocytes were 5,100. Sodium nitrite brought relief of the headache.

The fourth patient was not seen by Osler but he suggested the diagnosis after discussion with Dr. Lyon concerning Dr. Stockton's case in Buffalo. This was a Turkish Jew of 46 years, a shoemaker, whose chief complaints were general weakness, chronic headache, pain in the feet and legs made worse by walking, general diffuse pains in the abdomen, pain over the region of the heart, moderate chronic constipation, a slight cough and occasional attacks of shortness of breath. A deepening color of the skin had been noted first four years before. The red corpuscles, first counted on the day of death, were found to be 8,250,000. "The depth of color and darkness of the blood was far beyond the range of estimation for hemoglobin by the color scales of the various hemoglobinometers". The patient died "in collapse and after a few hours of drowsiness deepening into semiconsciousness". At autopsy the spleen, which had not been felt during life and which on percussion seemed smaller than normal, was found to be moderately enlarged. There was only moderate emphysema in the lungs, the heart was about normal and nothing definite was found to account for the condition.

It is of interest that the four cases reported by Osler typify so well the picture of polycythemia vera: the incidence in middle or late life, the somewhat greater frequency in males, the high incidence in Jews, the presence of symptoms such as headache, vertigo, constipation, weakness and vascular disturbances, the finding of splenomegaly in many cases, and the occurrence of leucocytosis in some cases in addition to polycythemia.

Analysis of his own and of five cases reported in the literature led Osler to no conclusion concerning the nature of the disease. While the clinical picture was certainly very distinctive, the symptoms, he pointed out, were somewhat indefinite and the pathology quite obscure. He suggested that a careful study be made of all forms of chronic cyanosis with polycythemia, particularly of those associated with heart disease and emphysema. There are essentially only two conditions, he remarked, other than the entity under discussion which permit patients to walk into the hospital or into the consulting room in spite

of the presence of extreme cyanosis, namely congenital heart disease and emphysema. Osler recommended more accurate study of the blood, measurement of the blood volume, its viscosity and specific gravity, the amount of hemoglobin and the diameter of the red corpuscles. He was inclined to attribute the cyanosis to an increased viscosity of the blood with resulting difficulty of flow. He raised the question whether the splenomegaly might not be simply the effect of chronic passive congestion. He closed with the statement that future investigation should determine whether one were dealing here in reality with a new disease.

In Osler's second paper, which appeared in the British Medical Journal (11), the "Chronic Cyanotic Polycythaemia with Enlarged Spleen" in which he had become interested was distinguished from that caused by primary tuberculosis of the spleen. Several observers had pointed out that cyanosis and polycythemia may be associated with this rare form of tuberculosis. Osler called attention to the chronic course of true polycythemia and the failure to demonstrate caseous masses or miliary tubercles in the enlarged spleens in the three cases of his series in which autopsy had been performed.

The clinical lecture on "Erythraemia (polycythemia with cyanosis—maladie de Vaquez)", delivered at the Radcliffe Infirmary, Oxford, on November 28, 1907, and published in the Lancet of January 18, 1908 (12) furnished a comprehensive picture of the disease which has not been amplified to any significant degree since that time. By 1908 reports had appeared not only in France, the United States and the British Isles but also from Vienna, Wiesbaden, Budapest, Berlin and elsewhere. At least 70 cases were on record.

Osler made quite clear that priority of description rested with Vaquez and was inclined to favor the use of the name, erythremia, for the disorder following the suggestion of Türk (13) of Vienna. He discussed the "torpor, mental and physical" which characterize these patients and he noted that the first patient he had seen in the hot summer days would be "red as a rose" and look bursting with blood, while in the winter he became "as blue as indigo." Osler was very much impressed with the degree of vasomotor instability seen in many cases. He stated that "high blood pressure is the rule" and sclerosis of the superficial arteries and a trace of albumin are frequently noted, and

that attacks of bronchitis and of asthma had been described. Hemorrhages, sometimes petechial, or hemoptysis, hematemesis or hematuria, had occurred in a number of cases. Death from cerebral hemorrhage had been noted in several instances.

The analogy with leukemia was drawn but, curiously enough, not on account of the changes in the leucocytes which may be so striking in some cases of polycythemia vera but rather because of the great increase in blood volume which Haldane had noted in cases of this disease and which Osler assumed takes place also in leukemia.

In further considering the pathology of "this interesting affection," Osler pointed out that the suggestion that the polyglobulism is due to retarded destruction cannot be considered seriously since there are no clinical or anatomical facts in support of such a view. The intense hyperplasia of the bone marrow was noted and by this time Osler accepted the view that the spleen participates actively in the process, for histological studies had not indicated that the enlargement was due to the accumulation of the products of hemolysis. He remarked, "Nothing is more certain—in the microcosm as in the macrocosm, given a demand and there is soon a supply. But here is a condition in which so far as we know there is an oversupply without any corresponding demand and the same riddle confronts us as in leukemia and several other diseases of which overproduction of a normal tissue or element is the essence." Osler discussed the suggestion made by Korányi and Bence that the disease is due to a lessened power of the red blood corpuscles to absorb oxygen, as well as Saundby's proposal that "there is such a state of capillary dilatation with slowing of the blood current that each little boatlet of blood cannot discharge its proper cargo and to make up for this failure more are put into circulation, the antithesis of the condition existing at high altitudes when as each little boatlet cannot get a sufficient cargo of oxygen in the space of time it remains in the lung capillaries, three are sent out to do the work for which two usually suffice."

Repeated bleedings were recommended by Osler for the fullness of the head and vertigo. Therapeutic procedures which he thought worthy of trial included the inhalation of oxygen and irradiation over the spleen.

In relation to Osler's comment concerning the blood pressure in poly-

cythemia, note may be made of the subsequent description by Gaisböck (14) of a group of cases in which hypertension was present, as well as albuminuria, in the absence of splenic or hepatic enlargement. There is reason to doubt that this represents a special form of erythremia. Parkes Weber (15), one of several clinicians who, following Osler, devoted much attention to this disorder, emphasized that hypertension is unusual in erythremia. Many have noted that cardiac hypertrophy is relatively uncommon. Peacock (16) showed that increases in blood volume or viscosity do not cause an increase in blood pressure. It has also been demonstrated that a decrease of the polycythemia in cases in which hypertension exists does not necessarily cause a fall in blood pressure.

Osler referred to the occurrence of erythromelalgia and was impressed with the association of vascular disease with erythremia, topics which have since received additional consideration (17, 18). Following Osler, important papers were published in the succeeding years by Weintraud (19), Lommel (20), Senator (21), Hirschfeld (22) and Mackey (23) and the first complete post mortem examination was reported by Weber and Watson (24). By 1912, Lucas (25) found published records of 189 cases, of which 123 can be accepted without any doubt as cases of erythremia.

One significant feature failed to impress Osler. This was the leucocytosis and the other signs of increased bone marrow activity which are so often encountered in erythremia. A leucocyte count greater than 10,000 per c.mm. was present in half of Osler's patients. He also did not recognize the fact that the platelets may be increased in this disease. Türk, whose proposal that the disorder be named "erythremia" was accepted by Osler, pointed out as early as 1902 that evidence of a combined increase of erythropoiesis and leukopoiesis is an important characteristic of the condition.

Studies conducted since Osler's time have yielded quantitative data supporting many of the assumptions he made but have produced remarkably little in addition (2). Thus, measurements of the blood viscosity have shown it to be 5 to 8 times the normal and the specific gravity of the blood has been found to be 1.075 to 1.080 (normal 1.055 to 1.065). The total mass of red cells has been shown to be greatly increased. It has been demonstrated that the total blood volume is

greater than normal although it is not as much increased as would be expected from the gain in red cell mass, there being, in most instances, a reduction in plasma volume.

It has been shown, also, that the circulatory minute volume and the velocity of the blood flow are decreased. The skin capillaries have been found to be distended and enlargement of part or all of the capillary loops has been noted, particularly in the venous segments. All of the available vessels, in short, are open in this disease. Brown and Giffin (26) pointed out that the additional vascular space in the skin leads to a loss or impairment of the physiological heat mechanism with the result that many sensory symptoms such as intolerance to heat and cold and burning sensations develop.

Osler's conclusion that erythremia cannot be attributed to decreased destruction of the red cells found support in studies of the pigment metabolism in this disease (32). These indicated that, if anything, blood destruction is exaggerated. It was suggested later that an increased corpuscular "life span" might account for the disorder but, so far, no adequate data have been offered in support or in contradiction of this hypothesis. As already quoted, Osler was intrigued by the fact that here was a condition "in which so far as we know there is an oversupply without any corresponding demand." The cause of this increased activity of the hemopoietic system is as obscure today as it was in Osler's era. The factors which govern the physiologic regulation of hematopoiesis are still unknown and it is still a mystery why and how the blood remains "normal."

The respiratory minute volume has been found to be increased and the vital capacity reduced, the latter perhaps as the result of the intense pulmonary vascular congestion. The observation that the oxygen saturation of the arterial blood is within physiological bounds has been confirmed recently (27), even in cases with volumes of packed red cells as high as 81 per cent. The hemoglobin is normal in all respects in this disorder and the oxygen unsaturation of the venous blood is within normal limits (28). The contradictory report (29) that the hemoglobin in polycythemia vera does not give up its oxygen as readily to the tissues as does normal blood has found no support in more recent studies (30). There is also nothing to confirm the suggestion (31) that there is a decrease in the pulmonary permeability to oxygen. It has

been reported that during exercise there is a significantly increased arterial oxygen unsaturation (31) but these observations await duplication.

It follows that the abnormal color of the skin is due to the color the blood assumes when an abnormally large proportion of reduced hemoglobin is present. The vascular tree being filled to its greatest capacity and there being marked slowing of the blood flow, cyanosis occurs, but its intensity depends on the number and distribution of the peripheral capillaries and the subcapillary venous plexuses as well as on the thickness and amount of pigmentation of the skin.

Osler was led by his thoughts concerning "oversupply without any corresponding demand" to draw an analogy with leukemia. Consistent with this view are the cases in which a very striking leukocytosis is present and immature myeloid leukocytes are found in the circulation; those instances in which, in spite of a clinical and hematologic picture of erythremia, at autopsy the amount of leukoblastic tissue and all the pathologic findings closely resembled those characteristic of chronic myelocytic leukemia; the cases in which, after a variable duration with a course typical of erythremia, anemia developed while the leukocytosis remained high or became still greater; the cases of erythremia terminating in a classical picture of acute myeloblastic leukemia; and, finally, the cases of chronic myelocytic leukemia in which the later course and clinical picture were those of erythremia (2, 33). The Italian school of hematologists (Ferrata, Di Guglielmo) strongly support the concept that erythremia and leukemia depend on a single pathologic factor which, in erythremia, consists in a reversion on the part of the "clasmatocytoid hemohistioblast" (the primitive blood cell) to its embryonic activity so that it produces erythrocytes as well as leukocytes.

From time to time, however, attempts have been made to relate the development of erythremia to anoxia. Reference has been made already to the suggestion that the hemoglobin may be abnormal in that its oxygen combining power may be decreased. It has been proposed that the capillaries may be so dilated that the red cells cannot unload their oxygen or the tissues may be abnormal and tissue respiration may be increased. No adequate support for these hypotheses has been offered, however.

In erythremia, in contrast to secondary polycythemias, the percentage oxygen saturation of the arterial blood is normal. Consesequently, it should be clear that a theory of anoxia applied to this disease requires that anoxia be produced by circumstances local to the bone marrow. Consistent with this is the report of Reznikoff, Foot and Bethea (34) who observed marked narrowing and fibrosis of the arteries and arterioles in the bone marrow in certain cases of erythremia. It remains to be shown that these vascular and hematologic changes were etiologically related and not merely coincidental. Direct measurements of the oxygen saturation and tension of samples of blood removed from the sternal marrow cavity (35) have demonstrated no significant differences between normals, anemic patients and patients with erythremia. However, the techniques used were not adequate even to demonstrate a lowered percentage oxygen saturation of the marrow blood in anemia, where an anoxic stimulus is generally believed to be the cause of increased erythropoiesis. Consequently, these negative results cannot be regarded as denying a possible role of oxygen lack as a cause of erythremia.

The writer is inclined, nevertheless, to favor the view that erythremia is similar in its pathogenesis to leukemia and is not attributable to the influence of anoxia on the bone marrow. It is clear, however, that the subject of the pathogenesis of this disorder is an open one. It would seem worthwhile to reevaluate the significance of the variety of studies which have been reported hitherto and perhaps also to explore the subject experimentally. Thus the polycythemia produced in animals by feeding cobalt might be studied and its mechanism investigated. It might be of value to determine whether it is really true, as everyone assumes, that anoxia stimulates erythropoiesis by a direct effect on the bone marrow (36). It seems possible that the effect of rarefied atmospheres in stimulating erythropoiesis is mediated through some other organ. Discovery of such a hypothetical mechanism might prove of value in disclosing the factors governing hemopoiesis.

Although there has been so little progress since Osler's time in gaining an understanding of the pathogenesis of erythremia, advances in the management of the disorder, fortunately, have not been held to this slow pace. In addition to venesection, a procedure initiated in Osler's time and utilized effectively to this day, a variety of methods of treat-

ment have been devised. These include impairment of blood regeneration following venesection by feeding an iron-poor diet, destruction of the blood by the administration of phenylhydrazine, and destruction of hemopoietic tissue by roentgen irradiation, especially "spray" therapy (37), by the administration of nitrogen mustard (38) or by injecting radioactive phosphorus (P^{32}). Of these procedures, the last has achieved the most favored position.

Radioactive phosphorus passes to tissues which have a high phosphorus content and which metabolize phosphorus rapidly. Since the half-life of P^{32} is 14.3 days, steady irradiation of tissue takes place for several weeks. The concentration of radioactive phosphorus in bone makes it particularly valuable in the management of hemopoietic disorders and, of these, the most impressive beneficial effects have been observed in erythremia. Lawrence (39), in a series of 115 cases, reports satisfactory clinical and hematological remissions lasting a number of years. Many of his patients received only one course of therapy (usually 2 injections of 3–6 mc.), some of them not needing retreatment after 4, 5, 6, 7 and 8 years. The average duration of life in his cases has been approximately 17 years, a life expectancy similar to that of patients with diabetes mellitus treated with insulin and of patients with pernicious anemia treated with liver extract. Hall (40), in a series of 124 cases, noted a reduction of hemorrhagic manifestations from 33 to 1.6 per cent, while the incidence of thrombosis decreased to 2.4 per cent from 27.4 per cent. In each series, however, acute leukemia was observed 5 times, an incidence which is higher than had been noted prior to the use of this therapeutic agent (41).

REFERENCES

1. Quoted from Dreyfus, C., An historical survey of the clinical picture of plethora vera, Bull. New Eng. Med. Center, **5**, 10, 1943.
2. Harrop, G. A., Jr. and Wintrobe, M. M., Polycythemia, *in* Handbook of Hematology, edited by Hal Downey, 1938, New York, Paul B. Hoeber, Inc., Vol. IV, sec. 34, pp. 2366–2444.
3. Viault, F., Sur l'âugmentation considérable du nombre des globules rouges dans le sang chez les habitants des hautes plateaux de l'Amerique due Sud, Compt. rend. Acad. d. sc., **111**, 917, 1890.
4. Vaquez, H., Sur une forme spéciale de cyanose s'accompanant d'hyperglobulie excessive et persistente, Compt. rend. Soc. de biol., **4**, 384, 1892 and suppl. note, Bull. et mém. Soc. méd. d'hôp. de Paris, 3 ser., **12**, 60, 1895.

5. CABOT, R. C., A case of chronic cyanosis without discoverable cause, ending in cerebral hemorrhage, Boston M. & S. J., **141,** 574, 1899.
6. MCKEEN, S. F., Case of marked cyanosis, difficult to explain, Boston M. & S. J., **144,** 610, 1901.
7. SAUNDBY, R. AND RUSSELL, J. W., An unexplained condition of chronic cyanosis, with a report of a case, Lancet, **1,** 515, 1902.
8. CUFFER AND SOLLIER, Diathese congestive veineuse et congestion veineuse generalisée, Rev. de méd., **9,** 825, 1889.
9. VAQUEZ, H. AND QUISERNE, De la polyglobulie progressive comme signe pronostic dans les cyanoses congenitales, Compt. rend. Soc. de biol., **54,** 915 and 1073, 1902.
10. OSLER, W., Chronic cyanosis with polycythemia and enlarged spleen; a new clinical entity, Am. J. Med. Sci., **126,** 187, 1903.
11. OSLER, W., Chronic cyanotic polycythemia with enlarged spleen, Brit. Med. J., **1,** 121, 1904.
12. OSLER, W., A clinical lecture on erythraemia, Lancet, **1,** 143, 1908.
13. TÜRK, W., Beiträge zur Kenntnis des Symptomenbildes: Polyzythämie mit Milztumor und "Zyanose", Wien. klin. Wchnschr., **17,** 153, 189, 1904.
14. GAISBÖCK, F., Die Polyzythämie, Ergebn. d. inn. Med. u. Kinderh., **21,** 210, 1922.
15. WEBER, F. P., Polycythaemia, Erythrocytosis and Erythraemia (Vaquez-Osler Disease), London, H. K. Lewis & Co., 1921.
16. PEACOCK, H. A., Blood pressure and blood volume in cases of polycythaemia vera, Proc. Staff Meet. Mayo Clin., **4,** 286, 1929.
17. BROWN, G. E. AND GIFFIN, H. Z., Peripheral arterial disease in polycythemia vera, Arch. Int. Med., **46,** 705, 1930.
18. NORMAN, I. L. AND ALLEN, E. V., The vascular complications of polycythemia, Am. Heart J., **13,** 257, 1937.
19. WEINTRAUD, W., Polyglobulie und Milztumor, Ztschr. f. klin. Med., **55,** 91, 1904.
20. LOMMEL, F., Über Polyzythämie mit Milztumor, Deutsch. Arch. f. klin. Med., **87,** 315, 1906.
21. SENATOR, H., Über Erythrocytosis megalosplenica, Ztschr. f. klin. Med., **60,** 357, 1906.
22. HIRSCHFELD, H., Erythrämie und Erythrocytose, Klin. Wchnschr., **44,** 1302, 1907.
23. MACKEY, L. G. J., Chronic splenomegalic polycythemia with report of a case, Birmingham M. Rev., n.s. **10,** 113, 1907.
24. WEBER, F. P. AND WATSON, J. H., Chronic polycythaemia with enlarged spleen, probably a disease of the bone marrow, Trans. Clin. Soc., London, **37,** 115, 1904; also: Internat. Clinics, s. 14, **4,** 47, 1905.
25. LUCAS, W. S., Erythremia or polycythemia with chronic cyanosis and splenomegaly, Arch. Int. Med., **10,** 597, 1912.

26. Brown, G. E. and Giffin, H. Z., The skin capillaries in polycythemia vera, Am. J. Med. Sci., **166,** 489, 1923.
27. Wasserman, L. R., Dobson, R. L. and Lawrence, J. H., Blood oxygen studies in patients with polycythemia and in normal subjects, J. Clin. Investigation, **28,** 60, 1949.
28. Isaacs, R., Pathologic physiology of polycythemia vera, Arch. Int. Med., **31,** 289, 1923.
29. Bansi, H. W. and Groscurth, G., Veränderungen der Sauerstoffbindungskurven des Blutes bei Stoffwechsel und Blutkrankheiten (Anämie und Polycythämie), Ztschr. f. klin. Med., **113,** 560, 1930.
30. Altschule, M. D., Volk, M. C. and Henstell, H., Cardiac and respiratory function at rest in patients with uncomplicated polycythemia vera, Am. J. Med. Sci., **200,** 478, 1940.
31. Harrop, G. A., Jr. and Heath, E. H., Pulmonary gas diffusion in polycythemia vera, J. Clin. Investigation, **4,** 53, 1927.
32. Paschkis, K. and Diamant, M., Beiträge zur Pathologie der Erythrämie, Deutsch. Archiv. f. klin. Med., **169,** 180, 1930.
33. Wintrobe, M. M., Clinical Hematology, 2nd Edition, Philadelphia, Lea and Febiger, 1946.
34. Reznikoff, P., Foot, N. C. and Bethea, J. M., Etiologic and pathologic factors in polycythemia vera, Am. J. Med. Sci., **189,** 753, 1935.
35. Berk, L., Burchenal, J. H., Wood, T. and Castle, W. B., Oxygen saturation of sternal marrow blood with special reference to pathogenesis of polycythemia vera, Proc. Soc. Exper. Biol. and Med., **69,** 316, 1948.
36. Cartwright, G. E. and Wintrobe, M. M., Hematopoiesis, *in* Ann. Rev. Physiol., **11,** 335, 1949. Stanford, Cal., Annual Reviews, Inc., Victor E. Hall, Ed.
37. Richardson, W. and Robbins, L. L., The treatment of polycythemia vera by spray irradiation, New Eng. J. Med., **238,** 78, 1948.
38. Spurr, C. L., Smith, T. R. and Jacobson, L. O., Chemotherapy in human lymphomas, leukemias and allied disorders of the hemopoietic system, Radiology, **50,** 387, 1948.
39. Lawrence, J. H., The control of polycythemia vera by marrow inhibition. A ten year study on 152 patients. J. A. M. A. (in press).
40. Hall, B. E., Therapeutic use of radioactive phosphorus in polycythemia vera, leukemia, and allied diseases, *in* The Use of Isotopes in Biology and Medicine, 1948, Madison, The University of Wisconsin Press, p. 353.
41. Tinney, W. S., Hall, B. E. and Giffin, H. Z., Hematologic complications of polycythemia vera, Proc. Staff meet., Mayo Clin., **18,** 227, 1943.

A CONSIDERATION OF THE BANTI SYNDROME

"Even in well-known affections advances are made from time to time that render necessary revision of our accumulated knowledge, a readjustment of old positions, a removal even of the old landmarks."

SIR WILLIAM OSLER, 1895.

PHILIP F. WAGLEY*

From the Department of Medicine, The Johns Hopkins University and Hospital, Baltimore, Maryland

The purpose of this paper is to cite a few of the publications pertinent to the evolution of the concept of the Banti syndrome which have appeared since Osler's first reports (1–7) on the subject. Although originally considered a separate disease entity, the term is now applied to conditions of various etiologies having in common anemia, leukopenia, occasionally thrombocytopenia, splenomegaly and evidence of hepatic disease or altered portal circulation.

I

Incidence: Although relatively uncommon (8–10) such cases are the subject of numerous papers. The incidence has been reported equal in the two sexes (11–14). Occupation and heredity have been stated as playing no role (4, 11, 12). Cases indicating a possible familial incidence have been described (4, 9, 15) though Banti would not accept one such series (16) as an example of his entity. The condition seems to be more common in white than colored patients (17). The younger age group has predominated in several series (4, 9, 11, 17, 18, 19). No unusual geographic distribution has been noted (18, 20).

II

Symptoms and signs: The following paragraphs present in summary Banti's original description of his clinical observations. The sequence of events he recorded is rarely seen. The clinical symptoms and signs are simply those of anemia, splenomegaly, unusual bleeding (most frequently from esophageal varices), altered portal blood flow and liver disease; symptoms and signs which may be seen in a variety of diseases.

* Fellow in the Medical Sciences of the National Research Council.

EDINBURGH
MEDICAL JOURNAL.

ORIGINAL COMMUNICATIONS.

CHRONIC SPLENIC ENLARGEMENT WITH RECURRING GASTRO-INTESTINAL HÆMORRHAGES.

By WILLIAM OSLER, M.D., LL.D., F.R.S., *Professor of Medicine, Johns Hopkins University, Baltimore.*

EXCLUDING the enlarged spleen of leukæmia, chronic malaria, cirrhosis of the liver, heart disease, and rickets, the cases of so-called primitive enlargement of the organ fall into two groups.

First, a series in which the spleen is enlarged without causing any symptoms, other than those due to mechanical pressure. In the past few years I have seen four patients, all women, apparently in perfect health, who complained only of a feeling of pressure in the abdomen, in all of whom the spleen was much enlarged. In two cases in which the organ was freely movable and caused a great deal of discomfort, my colleague Halsted opened the abdomen and successfully packed the spleen in position with gauze, an operation much less serious than splenectomy and very efficacious. Both these patients have been seen more than two years subsequent to the operation, and have remained quite well. In a third case, a girl was sent into the gynæcological department, supposed to have an ovarian tumour. She was robust and strong, with good colour, and had been hard at work. She subsequently had a twist of the ligaments and sphacelus of the spleen, with enormous enlargement, adhesion to the abdominal wall, redness, and inflammation. The organ was freely incised by Halsted, and an enormous quantity of necrotic spleen tissue removed; the patient made a good recovery. This condition is, I think, more common than we suspect. The spleen is, as a rule, only moderately enlarged. In some cases there has been a history of past malaria, but in a majority the condition is one of, so far as we can tell, primary enlargement. It must not be forgotten that only a blood examination can determine whether or not such patients have leukæmia, since in this disease, as is well

Banti (19, 20, 21) described three clinical phases. Phase I was termed the preascitic or anemic stage. He believed that the enlargement of the spleen always preceded other signs and symptoms. Usually the onset was insidious with increasing pallor, easy fatigability, palpitation and dyspnea; occasionally there was ankle edema if anemia were severe. Epistaxes were frequent. Sometimes pain or a feeling of weight in the left hypochrondrium led to the discovery of a large spleen and anemia. Characteristically the spleen was not tender or painful (unless perisplenitis occurred). The splenic enlargement gradually increased until, infrequently, the organ reached the pelvic brim. Banti thought brief episodes of fever and chills were not uncommon in this period. Although he denied evidence of hepatic disease during this stage, his only clinical criteria were inability to detect hepatic enlargement, jaundice, evidence of portal collateral circulation or increased urobilin in the urine. In his opinion, this stage of the disease lasted usually from 1 to 4 years or longer. Phase II was ushered in by gradual enlargement of the liver until it extended two to three fingerbreadths below the costal margin. The anemia increased. No ascites was apparent. The spleen did not enlarge further. Jaundice was observed only occasionally, and was thought due to liver damage and not to increased blood destruction. The urine was found to contain urobilin and sometimes bilirubin. Banti thought this period lasted generally only a few months. Phase III was characterized by ascites, associated with a decrease in the size of the liver. Jaundice appeared. The spleen remained unchanged in size. Anemia increased in severity. Gastrointestinal hemorrhages were common. Urinary bile pigments increased in amounts. Death in these cases was ascribed to either gastrointestinal hemorrhage or hepatic insufficiency. Clinically Banti considered the third phase indistinguishable from atrophic (alcoholic) cirrhosis. He differentiated these cases from what he called splenic anemia because they progressed from a state of splenomegaly with anemia to one characterized by marked liver damage with cirrhosis, jaundice, collateral portal circulation and gastrointestinal hemorrhages.

Criticisms of Banti's original clinical description have been frequent. Eppinger (22) emphasized the extreme rarity of such a clinical history. In his wide experience he had seen only one possible case. McNee (23) stated that he never saw a case agreeing really closely with the sequence of events originally described. Furthermore, clinical states similar to the last or third phase as described by Banti have been observed in association with Laennec's cirrhosis (24), syphilis (7, 24, 26) "healed acute yellow atrophy" (27), schistosomiasis (28), hemochromatosis (27), post traumatic abdominal lesions (10, 12), aneurysms of the splenic artery (29, 30), cavernous transformations of the splenic vein (31), developmental anomalies of the portal system (30), thrombophlebitis of the portal and splenic veins (32), thrombosis of the splenic and portal system (12, 33, 34), persistence of the umbilical vein (35),

polycythemia (36), extension of the thrombosis of the umbilical vein at birth to involve the portal system (32, 37), obstruction of flow by periportal adhesions or extrinsic abdominal masses (34, 38) and infectious hepatitis (39). To expect one characteristic sequence of clinical events does not therefore seem logical. Rousselot (12) drew the conclusion that the clinical picture represents a heterogenous group of cases better called Banti's syndrome than Banti's disease.

Recurrent hematemesis or melena is not uncommon, occurring in about one-half of the cases diagnosed as Banti's syndrome (40, 41). Sometimes such gastrointestinal hemorrhage occurs without previous appearance of any other signs or symptoms (13). Epistaxes of severe degree in these cases are not infrequent (11, 19) and may be the only evidence of unusual bleeding (12). There seems to be no direct correlation between epistaxes and platelet count (12). Purpura occurs occasionally (4, 25, 42), may be recurrent (2) and associated with bleeding gums and ecchymoses (40).

Commonly, due to the enlarged spleen, the initial complaint concerns a mass in the abdomen (11). Usually, the spleen is quite firm and is not tender. Its size has been reported as varying inversely with the age of the patient (43). Splenic enlargement may decrease transiently after a severe gastrointestinal hemorrhage (12). Occasionally a friction rub or a thrill may be palpable over the spleen and a bruit may be heard (44). Transient, sometimes severe, abdominal pain occurs (11) and may be due to infarctions with perisplenitis or a twisted splenic pedicle. When hepatomegaly is present the enlargement is not great unless schistosomiasis is the etiological factor.

Although ascites occur in about one-third of the cases (14) enlargement of the peripheral abdominal vessels is rarely noted (11, 20). Osler (2) reported that one patient (Case IX) had three separate severe episodes of ascites though at autopsy there was no cirrhosis of the liver; Rolleston (44) observed ascites in the absence of cirrhosis. Ravenna (45) considering the possible etiology of the syndrome stressed the rapid disappearance and recurrence of ascites in certain cases.

In the presence of splenomegaly and ascites anorexia is common; nausea and vomiting and diarrhea are infrequent (12). Cardiac symtoms seldom appear unless the anemia is severe (12). Dyspnea, palpitation and precordial distress may then develop in that order. De-

pendent pitting edema of mild degree is common. Urinary symptoms are extremely rare although hematuria has been observed (2). Peripheral lymph-nodes are usually not enlarged. Weight loss in one series of twenty-two patients averaged only about five pounds (11). Osler (2) and Giffin (46a) commented on melanoderma in several of their cases. A skin biopsy of one such patient failed to reveal any iron-containing pigment. Such skin pigmentation may have resulted from extensive use of Fowler's solution which was then in therapeutic vogue. Spider hemangiomata (5, 39) have been described.

III

Laboratory Data: These indicate that there is nothing characteristic about the anemia, bone marrow or peripheral blood differential count.

Usually these cases show a moderate hypochromic or normochromic normocytic anemia (14, 46). Banti stated the red blood cells generally range from 3 to 4 million per cubic millimeter. In three large series of cases (4, 11, 17) the red blood cell count averaged 3.49 million per cubic millimeter and in two of the series the hemoglobin averaged 54 per cent with a color index of 0.62. The majority of Larrabee's forty-seven cases (27) showed a microcytic anemia but macrocytic anemia has been observed (14, 47, 48). Wright (48) reported a case displaying a transition from a hypochromic microcytic anemia to a macrocytic anemia. Poikilocytosis and anisocytosis are reported frequently and polychromatophilia occasionally. The reticulocyte count may be normal although reticulocytosis does occur (46, 49) particularly after hemorrhage. Although Banti emphasized the absence of nucleated red blood cells in the peripheral blood (19) these have been reported frequently with this diagnosis (11).

Banti observed leucopenia and granulocytopenia with occasional absolute decrease in lymphocytes. The monocytes may show a relative or even absolute increase (20). Blast forms of the white blood cells in the peripheral blood have not been described in any of several large series of cases (4, 11, 12, 17), although "myeloid immaturity" has been reported (50). The leucocyte count is usually below 5,000 (14), averaging 4,616 for the patients in four large series (3, 9, 11, 20). The white blood cell count may be as low as 320 per cubic millimeter (51). Following sudden hemorrhage the count may exceed 12,000

per cubic millimeter (2) and after splenectomy the white blood cell count may rise to very high levels and remain elevated for the remainder of the patient's life (12).

The platelet count is frequently decreased (42, 46, 52). Occasionally, however, it may be normal or relatively high (31, 53). Cases of Banti's syndrome with no decrease of platelet count have been called "thrombocythemic" by Rosenthal (25). He reported that in such cases splenectomy was followed by a very rapid rise and permanent elevation of the platelet count. In two of his cases the count remained over 1 million and in another it ranged from 600,000 to 800,000 for two and one-half years following splenectomy. Platelets two to four times normal size may be seen occasionally in the peripheral blood (25). The significance of the apparent lack of correlation between platelet counts and bleeding tendencies in such cases cannot be evaluated in the absence of simultaneous data on prothrombin times (25, 42). However, Morlock and Hall (42) have reported a case of hepatosplenomegaly associated with bleeding tendencies with a platelet count of 56,000 to 68,000 and a normal prothrombin time. Tocantins (54) concluded the bleeding tendency was due to both thrombocytopenia and hypoprothrombinemia. Even in the absence of the Banti syndrome liver disease may be associated with thrombocytopenia (42, 55–60). Increased capillary fragility has been observed (25).

Coagulation time and clot retraction, when studied, have been found usually within normal range (12, 46). However, Rosenthal (25) observed impaired clot retraction in a few cases and its actual absence in one. Osmotic fragility of the red blood cells is frequently normal (12, 61, 62). However, Boulton (49) observed increased osmotic fragility, though at the time the reticulocyte count was 30 per cent. McMichael (51) carried out osmotic fragility studies in fifteen cases. In six the fragility was normal, in seven it was decreased and in two it was increased, with hemolysis beginning at 0.55 per cent to 0.6 per cent saline.

Banti (20) reported in his autopsied cases an increase of the amount of "red" marrow with many nucleated red blood cells. Dock and Warthin (63) described an increased number of normoblasts in the marrow, numerous phagocytes containing blood pigment and an occasional giant cell. An increase in erythropoiesis has been observed by others

(2, 64). Segerdahl (65) has reported marrow from one case as hyperplastic with immature erythrocytic and normal myelocytic cells. Mendell et al. (66) reported there were no characteristic marrow changes in the three cases they studied. Hypoplasia of the marrow also has been described as characteristic (13). Limarzi et al. (50) reported in detail on the bone marrow and blood in several cases of Banti's syndrome. In the earliest stages the marrow displayed a myelocytic hyperplasia while in the peripheral blood there was a moderate anemia and leukopenia. Later in the disease the marrow showed maturation arrest of the myelocytic and megakaryocytic tissue with leukopenia, neutropenia and thrombocytopenia and myelocytic immaturity in the peripheral blood. In the last stages of the condition, when cirrhosis of the liver was severe, they observed marked immaturity of both the erythrocytic and myelocytic series.

IV

Pathogenesis: In the following paragraphs Banti's opinion of the pathogenesis of this syndrome is presented for its historical interest. The evidence for considering increased portal and splenic vein pressure as the "common denominator" is outlined, as well as the various possible causes for such hypertension that have been suggested. It is pointed out that if such portal or splenic vein hypertension occurs in these cases its relationship to the anemia, leukopenia and thrombocytopenia remains unexplained. Although blood loss from varices and impaired hepatic function have been considered important factors it is possible the spleen itself may have an etiological role. A variety of evidence is considered suggesting that the spleen may destroy cellular elements of the blood excessively, or may inhibit hematopoiesis. Several possible objections to these interpretations in this syndrome are then presented. No conclusion is warranted with the present evidence about the exact role of the spleen in this syndrome.

Originally Banti (21) considered the syndrome the result of a "poison" produced in the spleen. In his last long article (20) on the subject he stated that some "infectious" agent probably reached the spleen through the arterial blood supply and caused primarily periarteriolar lesions (which, when extensive, he called 'fibroadenie'). He maintained his original opinion that the splenic lesions and enlargement were not secondary to any liver disease and listed five reasons for differenti-

ating his entity from that of Laennec's cirrhosis (21). His reasons for considering liver disease as absent in the early stage have been presented and are not adequate in the light of present day knowledge. His main premise for considering the spleen an etiological factor was his impression that splenectomy was curative.

Banti listed three observations from which he concluded the anemia was not due to increased blood destruction: (1) Microscopic examination of the splenic juice rarely showed any phagocytosis of red blood cells. (2) There was no increased pigmentation in the organs at autopsy. (3) There was no increase in number of nucleated red blood cells in the splenic pulp or extramedullary erythropoiesis.

As early as 1904 Dock and Warthin (63), following observations on two cases of portal obstruction, expressed the opinion that the splenomegaly of Banti's syndrome was the result of obstruction of the portal and splenic veins. Wallgren (37), in a discussion of a variety of extrahepatic lesions associated with portal vein obstruction, pointed out the similarities between such cases and those diagnosed as Banti's syndrome. Several others (27, 38) described the Banti syndrome associated with various abdominal lesions obstructing the venous outflow of the spleen. Rousselot (12) and Thompson (34), after reviewing a large number of cases diagnosed as Banti's syndrome, came to the conclusion that venous obstruction was the "common denominator." Splenic vein pressures have been reported markedly elevated (67) in several cases of Banti's syndrome. In fourteen cases the splenic vein pressures ranged from 225 to over 500 millimeters of saline. However, twenty-two out of fifty-five carefully studied cases failed to show any obstructive factor (68).

Other possible causes of increased splenic vein pressure besides portal and splenic thrombosis have been described. Herrick (69) perfused normal and cirrhotic human livers through the hepatic artery under controlled pressures and measured the amount of fluid flowing from the portal vein. He concluded there was freer communication between the hepatic artery and portal vein in cirrhotic than in normal livers and that this communication probably was an important factor by which the arterial pressure could increase the portal pressure in the presence of cirrhosis of the liver. McIndoe (70) was unable to confirm Herrick's studies. However, Dock (71), on the basis of perfusion experiments, concluded that in cirrhosis there was damage to the intrahepatic arterioportal anastomoses and that in some cases the arterial pressure probably contributed significantly to the portal vein pressure.

Johnston (43) made camera lucida drawings of the terminal portal sheaths and the immediately accompanying hepatic arterioles in ten cases dying of acute infection and four previously diagnosed as Banti's syndrome. The average ratio in each case of hepatic artery lumen (Ha) to portal vein lumen (Pv) circumference was calculated (Ha-Pv) and found decreased in the Banti syndrome cases. There appeared to be no relationship between the changes in Ha-Pv ratio and fibrosis of the liver. Johnston concluded that constriction or reduction of the size of the portal venules was not simply the result of compression by contracting scar tissue since as much or more reduction was noted in livers with little fibrosis as in those most extensively sclerosed. The size of the spleen was inversely proportional to the size of available vascular bed. McMichael (72, 73) has suggested two other possible causes of increased portal pressure: (1) vasodilatation of the hepatic artery and arterioles and (2) vasospasm of the portal vein. Burton-Opitz (74) demonstrated sudden marked rises in portal pressure following the injection of small amounts of adrenalin into the portal vein of dogs. The slight rises in arterial pressure were not proportional and were more delayed. He interpreted this observation as supporting the idea that intrahepatic portal radicles have a constricting capacity. This conclusion has been substantiated by other experiments (75, 76). However, Popper (77) has shown that the walls of the portal vein radicles of man have much less smooth muscle than those of dogs.

Even if one assumes that elevated portal or splenic vein pressure is the "common denominator" in these cases, the actual mechanism of influence on the hematological tissues must be explained. Sturgis (14) considers the liver impairment and the blood loss from varices adequate reason for the anemia.

It has been assumed the elevated splenic vein pressures are associated with an increased amount of hemostasis in the spleen. Numerous experiments suggest that this may damage the red blood cell. Ham and Castle (78, 79, 80) have repeatedly emphasized the role of stasis in various anemias. Bolt and Heeres (81) demonstrated that red blood cells in the splenic vein showed decreased resistance to hypotonic saline. Heilmeyer (82) found that red blood cells become spheroidal during passage through the spleen. Bergenheim and Fah-

raeus (83) emphasized the effects of stasis in vitro and suggested the same effects might occur in the spleen. They found that incubation of defibrinated blood at 37°C. without stirring caused spherocytosis. From incubated serum Bergenheim and Fahraeus isolated a water-soluble, ether-insoluble, phosphorus-containing hemolysin. They assumed from further work with cobra venom containing lecithinase and enzyme inhibitors that "lysolecithin" was formed during sterile incubation of serum or citrated plasma. Two possibilities were suggested to explain the lack of spherocytosis occurring in incubated blood if it were continually agitated: either lysolecithin was not formed (presumably due to inhibition of serum lecithinase) or if formed, was immediately inactivated as a result of the circulation and contact of the serum or plasma with the red blood cells. Fahraeus (84) later quoted some of Knisely's experiments (85) to support his contention that such effects could occur in vivo in the spleen. Knisely studied the splenic vascular circulation of mice, rats and cats by direct visualization. He found the splenic sinuses capable of storing and concentrating red blood cells. Storage and concentration of red blood cells in the spleen of animals had been demonstrated previously by several other workers (86, 87, 88). Splenic storage of red blood cells may not be always intrasinusoidal (88a, 88b). Watson and Paine (89) were the first to show an increase in hematocrit in the splenic vein in man after the administration of adrenalin, thereby demonstrating a storage of red blood cells in the spleen. Among the nine cases they studied was one diagnosed as cirrhosis of the liver with congestive splenomegaly. Before injection of adrenalin the hemoglobin, hematocrit, red blood cell count and osmotic fragility of the red blood cells in blood removed simultaneously from the splenic artery and vein were practically identical. However, after the injection of adrenalin into the splenic artery, the splenic vein hemoglobin, hematocrit and red blood cell count rose dramatically and the osmotic fragility of the splenic vein red blood cells increased. Of even greater interest was the observation that the mean corpuscular hemoglobin concentration in the red blood cells of the splenic vein decreased. Watson and Paine suggested that during hemoconcentration and stasis in the spleen there was actual intracellular degradation of hemoglobin. A wide variety of other evidence has been interpreted as suggesting that the spleen is capable of alter-

ing and presumably damaging red blood cells passing through or stored within it. Rich and Rienhoff (90) observed a higher serum bilirubin content in the splenic vein than in the splenic artery, indicating red blood cell breakdown within the spleen. The lysolecithin content of splenic blood has been found higher than that in peripheral blood (47). Gripwall (91) isolated from the spleen a hemolytic substance similar in chemical properties to lysolecithin. Wasastjerna (92) reported that a heterologous anti-red blood cell serum with agglutinating and hemolyzing activity was more effective in normal than in splenectomized animals. Granick (93) observed an increase in non-hematin iron in red blood cells within the splenic tissue of horses.

However, the importance of the role of passive congestion in the spleen as an etiological factor in this syndrome has been questioned since the time of Banti himself. Dawson (94) reported that of one hundred and seven cases of thrombosis of the portal and splenic veins found at autopsy only thirty had splenomegaly, and of these only eighteen had had the clinical picture of "splenic anaemia". He concluded that such thrombosis of the portal and splenic system is not frequently associated with this syndrome. Attempts to produce it experimentally by interfering with the portal circulation have failed (72). Warthin (32) ligated the splenic vein but atrophy of the spleen resulted. Although Jager (95) produced slight splenic enlargement by intermittent splenic and collateral vein obstruction in dogs, the spleen never exceeded the dimensions attained in the initial congestion. Rousselot and Thompson (96) produced cirrhosis of the liver, splenic vein hypertension and splenic enlargement in dogs after repeated injections of silicon dioxide (silica) into the splenic vein. No hematological studies were reported. Burton-Opitz (74) stated in one of his numerous papers on experimental studies of the portal circulation that increases in portal vein pressure were not necessarily associated with any decrease in portal flow. McMichael (72) concluded from his observations and those of Jager (95) that enlargement of the spleen in excess of 500 grams in a human adult must involve some factor other than mere passive congestion. McMichael (72), Menon (97) and Cameron and deSaram (98) have insisted that hyperplasia of the pulp cells and endothelium indicates that some factor in addition to passive splenic congestion is of etiological importance.

Ravenna (45) concluded on the basis of six premises* that portal obstruction and splenic passive congestion were not necessary factors in this syndrome, but that instead, splenic arteriolar dilatation and active hyperemia occurred. As early as 1902, Barr (100) suggested that the splenic changes in Banti's syndrome were due to splanchnic vasomotor paresis. He reported marked alteration of the semilunar ganglia of his three cases: lymphocytic infiltration with fatty and pigment "degeneration" of the ganglia cells. If there were sufficient increase in arteriovenous communications and blood flow in the spleen to cause marked congestion and increased portal pressure the blood volume might increase. Blood volume determinations apparently have not been done with this possibility in mind. In support of a splenic arteriolar lesion are the observations reported by Bouchard during his discussion of one of Osler's papers (5) on splenic anemia. He had noted in some patients with cirrhosis of the liver and splenomegaly the simultaneous occurrence of a murmur over the spleen, clubbing of the fingers and numerous spider hemangiomata. He reported that the hemangiomata and splenic enlargement occasionally receded together.

Doan (101) has stated that, although the anemia observed in the Banti syndrome is probably due partially to blood loss from esophageal and gastric varices, increased sequestration and destruction of white blood cells and platelets in the spleen may account for the leucopenia and thrombocytopenia. He has been impressed by the relative lack of leucocytosis following severe gastrointestinal hemorrhage

* (1) Ravenna reported twelve cases of splenic and portal vein occlusion with out splenomegaly. (2) Some cases diagnosed as Banti's syndrome have not shown any obstruction in the portal system even though the splenic vein pressure was high. (3) Frequently lesions have been found about the splenic arterioles suggesting these may have been the primary site of change causing splenomegaly and elevated splenic and portal vein pressures. (4) By denervation of the spleen (99), splenomegaly has been produced in dogs, indicating again a splenic vascular change as a potential cause of such enlargement. (5) Transient recurrent episodes of ascites with sudden onset and rapid disappearance have been reported, suggesting a reversible process as the cause. (6) Lastly, Ravenna pointed out that dilatation of portal vessels may occur on the hepatic side of a localized obstruction in the splenic or portal vein indicating an increased and not such a decreased blood flow as one might logically assume to occur with thrombosis. He concluded that in such cases the thrombosis may have been secondary and not primary.

in such patients. Doan and Wright (102) stated that increased phagocytosis by splenic macrophages can be incriminated in all cases of "hypersplenism". Doan (103–105) and Wiseman and Doan (106) reported that the reticuloendothelial cells of the spleen may occasionally phagocytize red blood cells, platelets and granulocytes excessively in a selective or indiscriminate manner. Menon (97) observed increased erythrophagocytosis in the spleens of rabbits and rats previously injected with manganese chloride and senecionine. In 1911 Lintwarew (107) published some amazing pictures of extreme phagocytosis of red blood cells in both spleen and liver. However, in evaluating the significance of intracellular matter in macrophages studied in supravitally stained preparations of splenic tissue it must be remembered that a certain amount of phagocytosis may occur after death of the patient or surgical removal of the spleen. Rich (108) has shown that ingestion of red blood cells by macrophages can occur in vitro. Therefore, phagocytosis in such preparations may not necessarily indicate excessive phagocytosis in vivo. Von Haam and Awny (109), after studies on fixed smears stained by Giemsa's method and on smears stained by supravital techniques from cases of "hypersplenism", concluded there was some increase in number of endothelial cells and perhaps a slight increase in phagocytosis but the latter activity could not cause any great destruction of red blood cells, platelets or white blood cells.

Some observers have postulated a hypothetical effect of the spleen upon the bone marrow, presumably due to a splenic hormone (110). Shousboe (111) after studying a case of Banti's syndrome, concluded that the spleen controlled cell emission from the bone marrow. Before splenectomy his patient showed only occasional nucleated red blood cells in the periphery but, after splenectomy, and at comparable hemoglobin levels, 34 per cent of the nucleated cells in the peripheral blood were of the red blood cell series. Shousboe's conclusions from his bone marrow studies are, however, open to question because two of the sternal aspirations followed very severe gastrointestinal bleeding. Limarzi et al. (50), in their studies of the bone marrow in Banti's syndrome, found that, although a marked decrease in hyperplasia occurred after splenectomy, the anemia improved; they concluded that a maturation-inhibitory substance had been produced by the enlarged

spleen. Pearce, Krumbhaar and Musser (112) reported anemia of three to four months duration following splenectomy in dogs, and assumed that the transient anemia was due to a loss of some splenic factor which ordinarily stimulated erythropoiesis in the bone marrow. They felt they could shorten the period of anemia by the administration of splenic extracts. Leake and Bacon (113) followed the red blood cell counts over a period of several days following the administration of bone marrow and splenic extracts intravenously to rabbits and orally to dogs. They concluded that their extracts contained thermostable, water-soluble erythropoietic agents, which acted first by increasing the rate of production or delivery of existing erythrogenic centers and later caused an extension of the functioning red marrow. However, the hemoglobin levels did not change significantly in their studies. Stradomsky (114) cited the appearance of Howell-Jolly bodies in circulating red blood cells following splenectomy as evidence that the spleen affected maturation. Although Dameshek and Miller (115) suggested a possible hormonal mechanism inhibiting megakaryocytes from producing and releasing platelets in some cases of thrombocytopenic purpura, they found that in cases of splenic vein thrombosis and cirrhosis the megakaryocytes of the bone marrow were increased in number and platelet production seemed normal.

It should be pointed out that, if the spleen forms some factor inhibiting bone marrow activity, which, it has been suggested, may be formed in excess in cases of "hypersplenism", it seems odd that the spleen so frequently becomes one of the first sites of hematopoietic metaplasia. Furthermore, if the spleen forms some factor stimulating maturation, and inhibiting release, of very young hematopoietic cells it is rather contradictory that so many blast forms occur frequently in the peripheral blood in some cases in which the spleen has become one of the main sites of blood formation (116).

The suggestion (117) of streptothrix being demonstrable in the spleen and, therefore, being the cause of the Banti syndrome is of historical interest only; such histological appearances were not due to fungus (72). Nor are the experimental studies (118) on the possible relationship of infection to the syndrome admissable in light of present day knowledge.

V

Pathology of the spleen: According to the following descriptions the splenomegaly is frequently associated with microscopic evidence of recent or old hemorrhage, most marked around the penicillar arterioles which may be occluded. There is commonly an increase of connective tissue in the splenic pulp and around the malpighian follicles. The cellular elements of the pulp may or may not increase. The splenic vessels and portal vein may be dilated, tortuous and sclerotic and the veins may even be thrombosed. Whether such a histological picture is associated with any unusual splenic function is unknown.

Banti (19–21) described lesions in his cases in the spleen and liver, and frequently in the splenic and portal veins. He stated that, typically, the spleen was enlarged, smooth and of normal shape; the capsule was often unchanged or occasionally thickened; the weight was seldom below 1,000 grams but might be as large as 3 kilograms. On section the parenchyma appeared firm and red and the malpighian bodies were usually easily seen. Banti applied the term "fibroadenie" to the fibrosis observed around the malpighian follicles and thought that the fibrosis resulted from localized adenitis or inflammation of each follicle, extending into the pulp and follicle as the condition progressed until occasionally in the last stage some follicles became only sclerotic nodules. As the fibrosis of the splenic reticulum increased the splenic sinuses became smaller. During the second clinical phase Banti believed that intrahepatic branches of the portal vein became thickened and sclerosed. Cirrhosis of the liver was observed in the third and last phase of the disease and was considered by Banti as indistinguishable from the portal cirrhosis of Laennec. He did not observe siderosis in either the spleen or liver. Banti reported patches of "chronic sclerotic endophlebitis" in the splenic, portal and mesenteric veins, but, he did not describe complete thrombosis of the splenic or portal veins in any of his cases (23). As the most extensive lesions were usually seen in the perifollicular area and were occasionally associated with hyaline changes of the penicillar arterioles which supply the area, Banti assumed a lesion of the arteriole to be primary.

After studying some of the splenic sections from Banti's original cases Dürr (119) came to the conclusion that the changes described were indistinguishable from those seen in cases of hepatic cirrhosis.

MacCallum (120) described the appearance of the spleen from three patients of Osler's series (3). A few non-calcareous thrombi were found in the branches of the splenic veins of one case though the splenic vein itself appeared normal. Microscopically there was a great

increase in connective tissue in the pulp area. The malpighian follicles were less numerous than in a normal spleen but MacCallum suggested that the apparent diminution in number was due to the enormous increase in size of the red splenic pulp, consisting almost entirely of matted thick-walled venules. Many of the follicles were normal in appearance though some were very small; no sclerotic process as described by Banti was observed about them. Rounded mononuclear cells closely resembling plasma cells were abundant; eosinophils were numerous and polymorphonuclear cells and multinucleated giant cells were seen occasionally. MacCallum observed no extravasation of blood with hemosiderin formation and no marked widening of the venules. He did not think such splenic enlargement and induration simply followed chronic passive congestion. Menon (97), Cameron and deSaram (98) and Von Haam and Awny (109) have commented on the reticuloendothelial hyperplasia in the splenic pulp in cases of the Banti syndrome and have concluded that such a histological feature is not seen in simple chronic passive congestion of the spleen. Chaney (11) reported the average weight of the spleen in sixty-nine cases was 950 grams with extremes of 120 and 2290 grams. He observed splenic infarcts in five cases studied. The average diameter of the malpighian follicles was less than normal being 0.35 millimeters. Klemperer (121) stated that the size of malphighian follicles varies inversely with the age of the patient.

McMichael (72), after the pathological study of forty-five selected cases of splenomegaly, concluded they could be divided into two groups: (1) one in which cirrhosis of the liver was accompanied by splenomegaly and (2) one in which, although obvious cirrhosis of the liver was absent, the enlarged spleen showed pathological features identical with those in the first group. He described a variety of splenic lesions all of which he concluded derived from two types of changes: (1) hemorrhage about the penicillar arterioles which supply the perifollicular area and, (2) proliferation of reticuloendothelial cells. Sites of old hemorrhages called "siderotic nodules" were often visible grossly as rusty yellowish spots on the cut surface of the spleen and showed microscopically a small, central, frequently hyalinized, artery surrounded by a zone of connective tissue and masses of golden-yellow iron-containing pigment. Such lesions have been described by others and called "tobacco nodes of Gamma-Gandy" (121).

Moschowitz (122), assuming the splenomegaly of the Banti syndrome was always due to portal hypertension, listed the histological changes observed in the spleen at various stages following the onset of such hypertension. At first, hemorrhage about the malpighian follicles occurred and the sinuses were invisible because of engorgement of the pulp with red blood cells. Later dilated venous sinuses were observed which subsequently became smaller as proliferation of the cells in the intersinus pulp or Bilroth cord areas occurred and fibrosis appeared. The walls of the sinuses became progressively thicker and the pulp cells assumed more and more the appearance of fibroblasts. The fibrosis encroached on the follicles until they diminished markedly in size. Although the sinuses remained small they occasionally were so prominent in number that the sections resembled an angioma. Foci of hematopoieses were observed. Klemperer (121) has stated myeloid metaplasia is occasionally seen in the spleen in cases of splenic or portal vein thrombosis.

The possibility should be considered that the splenic lesion in some cases of so-called Banti syndrome may be comparable to the spider hemangiomata seen in the skin of some of the cases. However, increased splenic flow alone may not cause this syndrome for cavernous hemangiomata of the spleen, seen usually in adults before the age of 45 years, need not be associated with the symptoms of the syndrome (123) and the splenic tissue surrounding the hemangioma may be quite normal.

VI

Clinical course and therapy: The clinical course depends usually on the severity of gastrointestinal bleeding and the degree of liver damage. Statistically splenectomy appears the most effective treatment, though it is not always successful. The younger the patient and the less the degree of liver damage the more likely splenectomy will be beneficial.

Generally the clinical course occupies several years. Various signs and symptoms and laboratory data have been listed as indication for or against splenectomy. Hanrahan (13) concluded that, with evidence of an appreciable degree of liver damage, the late prognosis was rarely improved by splenectomy and this slight chance had to be weighed against a high immediate postoperative mortality. However, if there

were evidence of only slight hepatic damage, removal of the spleen arrested or delayed the cirrhotic process. In his experience, macrocytosis indicated a poor prognosis with or without operation, but the more marked the leukopenia and the lower the color index the more likely would splenectomy be beneficial. Chaney (11) reported twelve postoperative deaths in a series of sixty-nine and concluded cirrhosis of the liver and ascites increased the operative mortality. Of the twenty-one cases of splenectomy studied by Eliason and Johnson (124) eight died, three from "liver insufficiency" and three from gastric hemorrhage. They concluded splenectomy in Banti's syndrome had best be done in an early stage and was indicated later only if the size of the spleen made the patient's life miserable.

Rosenthal (25) reported that in those cases with normal or relatively high platelet counts thromboses following splenectomy were frequent and occasionally fatal. In such cases the platelet counts rose postoperatively and remained at very high levels for several years. In the thrombocytopenic group, however, the platelet counts began to fall in the third postoperative week and remained at normal or only slightly increased levels. Rosenthal concluded that a relatively normal platelet count was a definite contraindication to splenectomy. Klemperer (31), Evans (125) and Moore (53) have also emphasized the dangers of postoperative thrombosis in such cases. However, Whipple (24) and others (12, 126) have stated that such a correlation between preoperative platelet counts and postsplenectomy thromboses has not been apparent.

Rousselot (12, 68), assuming passive congestion of the spleen was the common etiological factor, concluded the indications for splenectomy and the long term prognosis depended on the nature and severity of the obstruction to splenic flow. In the presence of decompensated liver disease splenectomy was considered contraindicated. The late postoperative results in his cases with Laennec's cirrhosis, portal vein occlusion or stenosis were extremely poor (fourteen of seventeen died) but in other forms of cirrhosis, splenic vein thrombosis, and in the group in which no obstructive factor was found the results were considered good (seven of forty-two died). More recently Elliott (126a) also has reported that splenectomy is more effective in those cases where no obstructive factor is identified. In Rousselot's series of

twenty-one deaths, eight died within six months after operation and seven died from one to two years after operation, the longest interval between operation and death being over thirteen years. Postoperative hematemesis occurred in no case that had not had such a sign before operation. The two leading causes of death were hematemesis and hepatic insufficiency. Of eleven cases having hematemesis after splenectomy seven died from exsanguination. In three series of cases undergoing splenectomy the operative mortality ranged from 6 to 11.7 per cent (33, 41, 127, 128). Mayo (33, 127) stated that only a small percentage of patients who have had hemorrhages before splenectomy have them after operation. Three of his cases developed thromboses of the superior mesenteric and portal veins postoperatively superimposed on a recanalized splenic vein thrombosis. Davis (129) has also reported postsplenectomy portal vein thrombosis.

Pemberton (41) reviewed one hundred and sixty-seven cases of splenic anemia and Banti's syndrome which were subjected to splenectomy. Of the one hundred and fifty-one patients surviving the immediate effects of the operation (operative mortality of 9.6 per cent) eighty were living at the time of the followup, three of them eighteen years after operation. Fifteen were still living ten to fifteen years after operation while ten of the sixty-eight patients surviving the operation but dying later lived for more than nine years. Although many of the causes of death were not attributable to the disease itself more than a third were directly attributable to hemorrhage. The operative mortality of those younger than forty years was only half that of the patients over forty years of age. Pemberton concluded that operation was of great benefit in many instances even in the late stages of the disease and that increased hepatic regeneration occurred following splenectomy. There seems to be general agreement that if splenectomy is of value its effect is more marked if performed early in the clinical course and before there is prominent evidence of liver disease (13, 17, 33, 127, 94, 24, 11, 124, 130). Mayo (33) stated splenectomy was the only curative treatment and Banti (20) thought splenectomy prevented progression of liver disease.

However, McMichael (51), in a study of ten cases before and on the average of two years after splenectomy found the hemoglobin concentration to have changed only from an average of 53.3 per cent to one of

64.8 per cent. Furthermore, he found in a series of thirty-seven cases of splenectomy that the mortality was 30 per cent. He also observed cases in which liver disease continued to progress after splenectomy, leading to a fatal termination. Giffin (46a) also reported one case developing clinical evidence of cirrhosis of the liver one year after splenectomy. Sturgis (14) concluded that there was no advantage from splenectomy and the idea that splenectomy averted liver disease was untenable.

Bryce (126) and Evans (125) recommended splenic artery ligation in this condition. Such ligation has been successfully done with apparent recovery from the signs and symptoms (131). However, in one patient so treated, although gradual diminution of the spleen size occurred with a concomitant increase in leukocyte level, the symptoms persisted; the clinical course with recurrent esophageal hemorrhages and progressive hepatic cirrhosis was not altered (101). Ligation of the splenic artery should be followed by transection to prevent recanalization. Coronary vein ligation and omentopexy have been used to supplement splenectomy (41). Injection of esophageal varices with sclerosing fluids after splenectomy has been suggested by Tocantins (54). Portal shunt operations have been recommended (132). Although deep x-ray and radium have been used over the spleen such treatment is said to be ineffective (101).

Medical therapy has been considered (14) as successful as splenectomy. Diets with ample amounts of proteins and including yeast or whole liver with large amounts of iron have been recommended. Davidson (133) observed marked rises in hemoglobin following oral iron therapy. In the five patients he studied the hemoglobin rose from an average of 30 per cent to one of 80 per cent. One splenectomized patient's hemoglobin remained at 45 per cent until iron was given, following which the hemoglobin rose to 94 per cent. Such observations are excellent evidence that blood loss may account to a great extent for the anemia in some cases. DeLangen (61) found impaired iron absorption in one case that improved after splenectomy.

CONCLUSION

The Banti syndrome is characterized by anemia, leukopenia, occasionally thrombocytopenia, splenomegaly and evidence of hepatic

disease or altered portal circulation. It is associated with a variety of diseases. Although splenic vein hypertension has been seen frequently in this condition and may be due to several different changes in the portal and splenic vascular system the role such hypertension plays other than leading to the formation of gastrointestinal varices and subsequent blood loss is unexplained. However, evidence for and against two suggested roles of the spleen in this syndrome have been quoted: increased damage to the red blood cells within the enlarged spleen and a humoral effect on the bone marrow by the spleen. The most effective therapy, particularly in the early stages and in younger patients, is apparently splenectomy, dietary treatment for cirrhosis, and supplementary iron orally.

BIBLIOGRAPHY

1. Osler, W.: Chronic Splenic Enlargement with Recurring Gastrointestinal Haemorrhages. Edinburgh Med. Jour. **47,** 441–453, 1899.
2. Osler, W.: On Splenic Anaemia. Amer. Jour. Med. Sci. **119,** 54–73, 1900.
3. Osler, W.: Anemia Splenica. Transactions Ass. Amer. Physicians **17,** 429–461, 1902.
4. Osler, W.: On Splenic Anaemia. Amer. Jour. Med. Sci. **124,** 751–770, 1902.
5. Osler, W.: Splenic Enlargements other than Leukaemic. Brit. M. J. **2,** 1151–1154, 1908.
6. Osler, W.: Splenomegaly; Two Attacks of Haematemesis; Irregular Liver. Proc. Roy. Soc. Med., London **7** (Clin. sect.) 108, 1914.
7. Osler, W.: Syphilis of the Liver with the Picture of Banti's Disease. Proc. Roy. Soc. Med., London **7** (Med. sect.) 1–7, 1914.
8. Webster, L. T.: Portal Thrombosis. Bull. Johns Hopkins Hosp. **32,** 16–19, 1921.
9. Kemp, R.: Recurrent Haematemesis in "Banti's Disease" Brit. M. J. **1,** 222–225, 1938.
10. Ravenna, P.: Splenoportal Venous Obstruction without Splenomegaly: Further Contribution to the Pathogenesis of Fibrocongestive Splenomegaly (Banti Syndrome). Arch. Int. Med. **72,** 786–794, 1943.
11. Chaney, W. C.: Splenic Anemia: A Clinical and Pathological Study of Sixty-nine Cases. Amer. Jour. Med. Sci. **165,** 856–875, 1923.
12. Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in so-called Banti's Syndrome: A Clinical and Pathological Study of Thirty-one cases with the Late Results Following Splenectomy. J. A. M. A **107** 1788–1793, 1936.
13. Hanrahan, E. M. and Vincent, B.: Surgery of the Spleen. Lewis System of Surgery **6,** chapter 15, 1937.

14. STURGIS, C. C.: Chronic Congestive Splenomegaly (Banti's Syndrome) Oxford Medicine **2,** 680(21)-680(27), 1947.
15. LUDBROOK, S. L.: Familial Splenic Anaemia. Arch. Dis. Childhood **6,** 239–244, 1931.
16. BASTAI, P.: Splenomegalia con cirrosi epatica familiare. Haematologica **3,** 370–412, 1922.
17. HANRAHAN, E. M., JR.: Splenic Anemia. A Study of End-results with and without Splenectomy, based on Thirty-five Cases. Arch. Surg **10,** 639–698, 1925.
18. HORA, J.: Zur Frage der Milz venenstenose der kinder. Arch. fur Path. Anatomis **300,** 670–684, 1937.
19. BANTI, G.: Splenomegalie mit Lebercirrhose. Beitr. zur path. Anat. u. z. Allg. Path., Jena **24,** 21–33, 1898.
20. BANTI, G. AND TISSOT, R.: Uber Morbus Banti. Folia Haematologica **10,** 33–74, 1910.
21. BANTI, G.: La splenomégalie avec cirrhose du foie. La Semaine Medicale **14,** 318–319, 1894.
22. EPPINGER, H.: Die Hepato-Lienalen Erkrankungen (Pathologie der Wechsel beziehungen Zwischen Milz, Leber und Knochenmark), Julius Springer, Berlin, 1920. p. 325.
23. MCNEE, J. W.: Liver and Spleen: Their Clinical and Pathological Associations. Brit. M. J. **1,** 1017–1022, 1068–1073, 1111–1116, 1932.
24. WHIPPLE, A. O.: The Combined Spleen Clinic. Results with Medical and Surgical Therapy in Splenopathies. Surg. Gyn. and Obst. **64,** 296–303, 1937.
25. ROSENTHAL, N.: Clinical and Hematological Studies on Banti's Disease. I. The blood platelet factor with reference to splenectomy. J. A. M. A. **84,** 1887–1891, 1925.
26. EASON, J.: The Anaemias of Syphilis. Brit. M. J. **2,** 186–188, 1921.
27. LARRABEE, R. C.: Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease. Amer. Jour. Med. Sci. **188,** 745–760, 1934.
28. ALMY, T. P. AND HARPER, J. G. M.: Banti's Syndrome apparently due to Infection with Schistosomi mansoni. J. A. M. A. **126,** 703–705, 1944.
29. MACHEMER, W. L. AND FUGE, W. W.: Aneurysm of the Splenic Artery. Arch. Surg. **39,** 190–204, 1939.
30. TRIMBLE, W. K. AND HILL, J. H.: Congestive Splenomegaly (Banti's Disease) due to Portal Stenosis without Hepatic Cirrhosis; Aneurysms of the Splenic Artery. Arch. Path. **34,** 423–430, 1942.
31. KLEMPERER, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease. Arch. Path. **6,** 353–377, 1928.
32. WARTHIN, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anaemia and Banti's Disease. International Clinics. **4,** 189–226, 1910.

33. MAYO, W. J.: Splenic Anaemia. Contributions to Medical and Biological Research: Dedicated to Sir William Osler **2,** 991–1001, 1919.
34. THOMPSON, W. P.: The Pathogenesis of Banti's Disease. Ann. Int. Med. **14,** 255–262, 1940.
35. ARMSTRONG, E. L., ADAMS, W. L., JR., TRAGERMAN, L. J. AND TOWNSEND, E. W.: The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of Two Additional Cases. Ann. Int. Med. **16,** 113–151, 1942.
36. ERF, L. A. AND JONES, H. W.: Radiophosphorus—an Agent for the Satisfactory Treatment of Polycythemia and its Associated Manifestations; a report of a case of polycythemia secondary possibly to the Banti Syndrome. Ann. Int. Med. **19,** 587–601, 1943.
37. WALLGREN, A.: Contribution á l'étude des splénomégalies de l'enfance (Pyle'phlébostenose splénique). Acta Paediatrica. Suppl. **6,** 1–122, 1927.
38. BRAHME, L.: Ein Fall von chronischen Portahindernis. Acta med. Scand. **61,** 175–193, 1924.
39. FISHER, R. L. AND ZUCKERMANN, M.: Banti's Syndrome Following Prolonged Infectious Hepatitis. A Report of Two Cases. Amer. Jour. Dig. Dis. **13,** 361–366, 1946.
40. KRUMBHAAR, E. B.: Banti's Syndrome (Splenic Anemia). Textbook of Medicine edited by R. L. Cecil. Saunders, Philadelphia, 1944. p. 954–956.
41. PEMBERTON, J. DEV.: Results of Splenectomy in Splenic Anemia, Hemolytic Jaundice and Hemorrhagic Purpura. Collected Papers of the Mayo Clinic and the Mayo Foundation **23,** 639–650, 1931.
42. MORLOCK, C. G. AND HALL, B. E.: Association of Cirrhosis, Thrombopenia and Hemorrhagic Tendency. Arch. Int. Med. **72,** 69–77, 1943.
43. JOHNSTON, J. M.: The Relation of Changes in the Portal Circulation to Splenomegaly of the Banti's Type. Ann. Int. Med. **4,** 772–781, 1931.
44. ROLLESTON, H. D.: A Clinical Lecture on Splenic Anaemia. The Clinical Journal **19,** 401–410, 1901–02.
45. RAVENNA, P.: Banti Syndrome (Fibrocongestive Splenomegaly) Definition, Classification and Pathogenesis. Arch. Int. Med. **66,** 879–892, 1940.
46. WINTROBE, M. M.: Clinical Hematology. Lea and Febiger, Philadelphia, 1946. p. 766–770.
46a GIFFIN, H. Z.: Clinical Observations Concerning Twenty-seven Cases of Splenectomy. Amer. Jour. Med. Sci. **145,** 781–795, 1913.
47. SINGER, K., MILLER, E. B. AND DAMESHEK, W.: Hematologic Changes Following Splenectomy in Man with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin. Amer. Jour. Med. Sci. **202,** 171–187, 1941.
48. WRIGHT, D. O.: Macrocytic Anemia in Banti's Disease. Ann. Int.Med. **8,** 814–824, 1935.
49. BOULTON, J. H.: The Distribution Curve of Erythrocyte Fragility: A Differ-

ent Method of Presentation of Fragility of Erythrocytes to Hypotonic Saline, with Preliminary Remarks on the Function of Reticulocytes. Blood **4,** 172–178, 1949.

50. Limarzi, L. R., Jones, R. M., Paul, J. T. and Poncher, J. G.: Sternal Marrow in Banti's Syndrome and other Splenomegalic States. Amer. Jour. Clin. Path. **13,** 231–248, 1943.
51. McMichael, J.: Splenic Anaemia. Transactions of the Medico-Chirurgical Society and Obstetrical Society of Edinburgh **114,** 97–116, 1934–35.
52. Frank, E.: Die Splenogene Leuko-Myelotoxikose II. Die Ruckwirkung von Milzbestrahlung und Milzextirpation aus das Weisse Blutbild bei Morbus Banti. Berl. klin. Wochenschrift **15,** 573–576, 1917.
53. Moore, S. W.: Portal Thrombosis Following Splenectomy for Splenic Anemia. Surg. Gyn. and Obst. **63,** 382–384, 1936.
54. Tocantins, L. M.: The Hemorrhagic Tendency in Congestive Splenomegaly (Banti's Syndrome). J. A. M. A. **136,** 616–621, 1948.
55. King, R. B.: The Blood Picture in Portal Cirrhosis of the Liver. A Report based on One Hundred Cases. New England J. Med. **200,** 482–484, 1929.
56. Howar, B. F.: Hematologic Studies in Liver Disease. J. Iowa Med. Soc. **28,** 148–150, 1938.
57. Abrami, P.: Le purpura des hepatiques. Ann de méd. **37,** 71–79, 1935.
58. Alt, H. L. and Swank, R. L.: Thrombopenic Purpura Associated with Catarrhal Jaundice: A Report of a Case. Ann. Int. Med. **10,** 1049–1054, 1937.
59. Alt, H. L., Carroll, H. B. and Doherty, C. C.: Thrombopenic Purpura Associated with Catarrhal Jaundice: Northwestern Univ. Bull. M. School **14,** 183–186, 1940.
60. Higgins, G. M. and Stasney, J.: The Peripheral Blood in Experimental Cirrhosis of the Liver. Folia haematologica **54,** 129–144, 1936.
61. deLangen, C. D.: One of the Forms of Anemia Splenica and the Function of the Spleen. Acta Med. Scand. **124,** 315–333, 1946.
62. Wagley, P. F.: Unpublished data.
63. Dock, G. and Warthin, A. S.: A Clinical and Pathological Study of Two Cases of Splenic Anaemia with Early and Late Stages of Cirrhosis. Amer. Jour. Med. Sci. **127,** 24–55, 1904.
64. Moore, R. A.: A Text Book of Pathology. Saunders, Philadelphia, 1945.
65. Segerdahl, E.: Ueber Sternalpunktionen. Acta Med. Scandinav. Suppl. **64,** 1–165, 1935.
66. Mendell, T. H., Meranze, D. R. and Meranze, T.: The Clinical Value of Sternal Bone Marrow Puncture. Ann. Int. Med. **16,** 1180–1196, 1942.
67. Thompson, W. P., Caughley, J. L., Whipple, A. O. and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome). J. Clin. Invest. **16,** 571–572, 1937.
68. Rousselot, L. M.: Congestive Splenomegaly. Bull. New York Acad. Med. **15,** 188–196, 1939.

69. HERRICK, F. G.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis. Jour. Exper. Med. **9,** 93–104, 1907.
70. MCINDOE, A. H.: Vascular Lesions of Portal Cirrhosis. Arch. Path. **5,** 23–42, 1928.
71. DOCK, W.: The Role of Increased Hepatic Arterial Flow in the Portal Hypertension of Cirrhosis. Trans. Ass. Amer. Phys. **57,** 302–306, 1942.
72. MCMICHAEL, J.: The Pathology of Hepatolienal Fibrosis. J. Path. and Bact. **39,** 481–502, 1934.
73. MCMICHAEL, J.: The Portal Circulation I. The Action of Adrenaline and Pituitary Pressor Extract. Jour. Physiol. **75,** 241–263, 1932.
74. BURTON-OPITZ, R.: The Vascularity of the Liver. *X*. The Influence of Adrenalin upon the Venous Inflow. Quart. Jour. Exper. Med. **5,**329–341 1912.
75. EDMUNDS, C. W.: Some Vasomotor Reactions of the Liver with Special Reference to the Presence of Vasomotor Nerves to the Portal Vein. J. Pharmacol. and Exper. Therap. **6,** 569–590, 1914–15.
76. MCMICHAEL, J.: The Portal Circulation. The Action of Acetylcholine. J. Physiol. **77,** 399–421, 1933.
77. POPPER, H.: Uber Drosselvorrichtungen an Lebervenen. Klin. Wochenschrift **10,** 2129–2131, 1931.
78. HAM, T. H. AND CASTLE, W. B.: Studies on Destruction of Red Blood Cells. Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias. Proc. Am. Philos. Soc. **82,** 411–419, 1940.
79. HAM, T. H. AND CASTLE, W. B.: Mechanism of Hemolysis in Certain Anemias: Significance of Increased Hypotonic Fragility and Erythrostasis. J. Clin. Invest. **19,** 788, 1940.
80. HAM, T. H. AND CASTLE, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis in Certain Anemias. Trans. Assoc. Am. Physicians **55,** 127–132, 1940.
81. BOLT, N. A. AND HEERES, P. A.: Der Einfluss der Milz auf die Roten Blutkorperchen. Klin. Wochenschrift. **1,** 1795–1796, 1922.
82. HEILMEYER, L.: Die Spharocytose als Ausdruck einer pathologischen Funktion der Milz. **179,** 292–306, 1936.
83. BERGENHEM, B. AND FAHRAEUS, R.: Uber spontane Hamolysin bildung im Blut, unter besonderer Berucksichtigung der Physiologie der Milz. Zeitschrift fur die Gesamte Experimentelle Medizin **97,** 555–587, 1936.
84. FAHRAEUS, R.: The Erythrocyte-Plasma Interface and the Consequences of Its Diminution. Lancet **2,** 630–634, 1939.
85. KNISELY, M. H.: Spleen Studies. I. Microscopic Observations of the Circulatory System of Living Unstimulated Mammalian Spleens. Anat. Rec. **65,** 23–50, 1936.
86. LAUDA, E.: Die normale und pathologische Physiologie der Milz. Urban and Schwarzenburg, Vienna, 1933 pps. 56, 226–271.

87. LAUDA, E. AND HAAM, E.: Zur Frage der Bedeutung der Milz als Blutkorperchen-reservoir. Zeitschrift fur die Gesamte Experimentelle Medizin. **80,** 640–661, 1932.

88. BARCROFT, J. AND ELLIOTT, R. H. E.: Some Observations on the Denervated Spleen. Jour. Physiol. **87,** 189–197, 1936.

88a. EMERSON, C. P., JR., SHEN, S. C., HAM, T. H., AND CASTLE, W. B.: The Mechanism of Blood Destruction in Congenital Hemolytic Jaundice. J. Clin. Investigation **26,** 1180, 1947.

88b. BJORKMAN, S. E.: Splenic circulation, with special reference to function of spleen sinus wall. Actamed. Scandinav. Suppl. 191, 1–89, 1947.

89. WATSON, C. J. AND PAINE, J. R.: A Study of the Splenic Venous Blood with Particular Reference to the Hematocrit Percentage and the Hemoglobin Concentration of the Erythrocytes, Before and After Splenic Arterial Injection of Adrenalin. Trans. Assoc. Amer Physicians **57,** 249–258, 1942.

90. RICH, A. R. AND RIENHOFF, W. F., JR.: The Bile Pigment Content of the Splenic Vein. Bull. Johns Hopkins Hospital **36,** 431–436, 1925.

91. GRIPWALL, A.: Zur Klinik und Pathologie des Hereditaren Hamolytischen Ikterus mit Besonderer Berucksichtigung des Verhaltens der Roten Blutkorperchen. Acta Med. Scand. Suppl. **96,** 1–290, 1938.

92. WASASTJERNA, C.: On the Influence of Immune Hemolysin on Red Blood Corpuscles in Vivo and in Vitro. Acta Med. Scand. **132,** 132–149, 1948.

93. GRANICK, S.: Non-hematin Iron in Erythrocytes. Proc. Soc. Exper. Biol. and Med. **53,** 255–256, 1943.

94. LORD DAWSON: A Paper on Indications for the Results of Removal of the Spleen. Brit. M. J. **2,** 699–700, 1932.

95. JAGER, E.: Uber Stauungsmilz. Verhandlungen der Deutschen Pathologischen Gesellschaft **26,** 334–342, 1931.

96. ROUSSELOT, L. M. AND THOMPSON, W. P.: Experimental Production of Congestive Splenomegaly. Proc. Soc. Exper. Biol. and Med. **40,** 705–708, 1939.

97. MENON, T. B.: The Splenic Reaction in Experimental Cirrhosis and in Pre-Cirrhotic Intoxication. J. Path. and Bact. **46,** 521–534, 1938.

98. CAMERON, G. R. AND DESARAM, G. S. W.: A Method for Permanently Dissociating the Spleen from the Portal Circulation (The "Marsupialized" Spleen) and its Use in the Study of Experimental Liver Cirrhosis. J. Path and Bact. **48,** 41–47, 1939.

99. HENSCHEN, C. AND HOWALD, R.: Die Anatomischen und klinisch-physiologischen Folgen der operativen Entnervung der Milz Experimentellen Untersuchungen. Arch. f. klin. Chir. **157,** 667–703, 1929.

100. BARR, J.: Three Cases of Banti's Disease. Lancet **2,** 493–497, 1902.

101. DOAN, C. A.: Banti's Syndrome. Modern Medical Therapy in General Practice (editor D. P. Barr), Williams & Wilkins, Baltimore **3,** 2945–2951, 1940.

102. Doan, C. A. and Wright, Claude-Starr: Primary Congenital and Secondary Acquired Splenic Panhematopenia. Blood **1,** 10–26, 1946.
103. Doan, C. A.: Pan-marrow Hematopoiesis (L. casei Factor) and Splenic Hematopenia: Experimental and Clinical Studies. Proc. Inst. Med. Chicago **16,** 178–201, 1946.
104. Doan, C. A.: Differential Diagnosis and Treatment of Diseases involving the Spleen. West Virginia Med. Jour. **41,** 121–129, 1945.
105. Doan, C. A.: Primary Splenic Pan-hematopenia. J. Lab. and Clin. Med. **30,** 385–388, 1945.
106. Wiseman, B. K. and Doan, C. A.: Primary Splenic Neutropenia. Ann. Int. Med. **16,** 1097–1117, 1942.
107. Lintwaren, J.: Die Zerstorungen der Erythrocyten in der Milz und der Leber unter normalen und pathologischen Verhaltnissen. Virch. Arch. **206,** 36–70, 1911.
108. Rich, A. R.: The Formation of Bile Pigment. Physiol. Rev. **5,** 182–224, 1925.
109. Von Haam, E. and Awny, A. J.: The Pathology of Hypersplenism. Amer. Jour. Clin. Path. **18,** 313–322, 1948.
110. Downs, A. W.: The Place of the Spleen in the Endocrine System. Blood **3,** 948–952, 1948.
111. Shousboe, J.: Two Cases of Splenic Control of the Cell Emission from the Bone Marrow. Acta Med. Scand. **103,** 123–136, 1940.
112. Pearce, R. M., Krumbhaar, E. B. and Frazier, C. H.: The Spleen and Anemia, Experimental and Clinical Studies. Lippincott, Philadelphia, 1918.
113. Leake, C. D. and Bacon, F. J.: A Preliminary Note on the Properties of an Alleged Erythropoitic Hormone. Jour. Pharmacol. and Exper. Therap. **23,** 353–363, 1924.
114. Stradomsky, B. N.: The Spleen as a Regulator of Blood Production. J. A. M. A. **68,** 885, 1917.
115. Dameshek, W. amd Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura, A Form of Hypersplenism. Blood **1,** 27–51, 1946.
116. Jackson, H., Jr., Parker, F., Jr. and Lemon, H. M.: Agnogenic Myeloid Metaplasia of the Spleen. New England J. Med. **222,** 985–994, 1940.
117. Gibson, A. G.: On Certain Cases of Splenomegaly and Banti's Disease. Proc. Roy. Soc. Med. **7,** (Med. Sect.) 7–9, 1914.
118. Hollins, T. J.: Primary Splenomegaly of Splenic Anemia: A Critical Study with Special Reference to the Pathogenesis. The Practitioner **94,** 426–462, 1915.
119. Dürr, R.: Bantimilz und hepato-lienale Fibrose. Beitrage zur Pathologischen Anat. u. Path. **72,** 418–455, 1924.
120. Cushing, H. and MacCallum, W. G.: Two Cases of Splenectomy for Splenic Anemia: A Clinical Lecture, January 1, 1920 to Third-Year Students, Tell-

ing an Old Story. A Report on the Pathologic Changes in Splenic Anemia (written in 1900 but not published). Arch. Surg. **1**, 1–22, 1920.

121. KLEMPERER, P.: The Pathologic Anatomy of Splenomegaly. Amer. Jour. Clin. Path. **6**, 99–159, 1936.
122. MOSCHOWITZ, E.: The Pathogenesis of Splenomegaly in Hypertension of the Portal Circulation; "Congestive Splenomegaly". Medicine **27**, 187–221, 1948.
123. AKCAKOYUNLU, I.: Capillary and Cavernous Hemangioma of the Spleen (Telangioma). Amer. Jour. Surg. **41**, 519–524, 1938.
124. ELIASON, E. L. AND STEVENS, L. W.: Surgery of the Spleen in Blood Dyscrasias. Surgery **13**, 177–187, 1943.
125. EVANS, W. H.: The Blood Changes After Splenectomy in Splenic Anaemia, Purpura Haemorrhagica and Acholuric Jaundice with Special Reference to Platelets and Coagulation. J. Path. and Bact. **31**, 815–832, 1928.
126. BRYCE, A. G.: Splenectomy and Thrombosis. Lancet **2**, 1423–1425, 1932.
126a. ELLIOTT, R. H. E.: Disorders of the Spleen with Special Reference to Those Amenable to Surgical Therapy. Bull. New York Acad. Med. **22**, 415–427, 1946.
127. MAYO, W. J.: Certain Blood Dyscrasias Dependent on Pathologic Conditions of the Spleen. J. A. M. A. **83**, 815–820, 1924.
128. LORD MOYNIHAN: Removal of the Spleen. Brit. M. J., **2**, 701–704, 1932.
129. DAVIES, J. C.: Splenic Anaemia and Portal Thromsosis. Lancet **2**, 498–500, 1928
130. ELIASON, E. L. AND JOHNSON, J.: Splenectomy. Surgery **2**, 823–834, 1937.
131. WATSON, R. B.: Ligation of Splenic Artery for Advanced Splenic Anaemia. Brit. M. J. **1**, 821–822, 1935.
132. BLAKEMORE, A. H. AND LORD, J. W., JR.: Technic of using Vitallium Tubes in establishing Portocaval Shunts for Portal Hypertension. Ann Surg. **122**, 476, 1945.
133. DAVIDSON, L. S. P.: Iron in the Treatment of Splenic Anaemia. Lancet **2**, 593–597, 1934.